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**The clinical application of Transcranial
Doppler Ultrasonography in infants and
children**

Dr DAY-EEL GOH

**Doctor of Medicine Thesis
University of Edinburgh
1994**



DEDICATION

This thesis is dedicated to my husband

Clifford Leen

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I am grateful for the opportunity to have carried out these studies during my tenure as a Research Fellow in the Department of Paediatric Neurology at the Royal Hospital for Sick Children, Edinburgh. This was made possible by the generous financial support received from the Earl of Elgin and Kincardine and the Trustees Savings Bank Foundation of Scotland.

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LIST OF ABBREVIATIONS

The following abbreviations have been used in the text:

CBF	- cerebral blood flow
CBFV	- cerebral blood flow velocity
CPB	- cardiopulmonary bypass
CPP	- cerebral perfusion pressure
CSF	- cerebrospinal fluid
CT	- computerised tomography
EDV	- end diastolic velocity
ICA	- internal carotid artery
ICP	- intracranial pressure
MAP	- mean arterial pressure
MCA	- middle cerebral artery
MFV	- mean flow velocity
MRI	- magnetic resonance imaging
M. meningocoele	- myelomeningocoele
ns	- not significant
PET	- photon emission tomography
pCO ₂	- arterial carbon dioxide tension
PI	- Gosling Pulsatility Index
PSV	- peak systolic velocity
rCBF	- regional cerebral blood flow
rCMRO ₂	- cerebral metabolic rate for oxygen
RI	- Pourcelot Resistance Index
RIe	- equilibrium resistance index
RIo	- initial resistance index
sd	- standard deviation
SPECT	- single photon emission computerised tomography
TCA	- total circulatory arrest
TCD	- transcranial Doppler
TCCD	- transcranial colour Doppler
VFR	- volume flow velocity response
VPS	- ventriculo-peritoneal shunt

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DECLARATION

I declare that this thesis has been composed by myself and that the work presented here is my own.

Candidate

ABSTRACT

Transcranial Doppler ultrasound (TCD) is a non-invasive, safe and readily repeatable technique of measuring cerebral blood flow velocity (CBFV) which may be ideally suited for the bedside assessment of cerebrohaemodynamic changes in children. A number of clinical conditions in which this technique could yield useful information was investigated i.e. in infants and children with hydrocephalus, pyogenic meningitis and during cardiopulmonary bypass (CPB) surgery. A range of normal CBFV values was first established from 51 normal children. Data on the peak-systolic (PSV), end-diastolic (EDV), mean flow (MFV) velocities and the Pourcelot Resistance Index (RI) was obtained in all TCD examinations. The RI is a ratio of the $(PSV-EDV)/EDV$. Where clinically indicated direct simultaneous measurements of intracranial pressure (ICP) was also performed to relate the observed changes in CBFV to ICP changes. In normal children after infancy, the RI remains stable throughout childhood while the MFV, PSV and EDV values are relatively stable over the first decade but decrease in the second decade of life.

In hydrocephalic patients a reduction in ICP with CSF drainage was associated with a decreased RI due to an increase in EDV which suggests that the RI reflects changes in distal cerebrovascular resistance. There was a significant correlation between RI and ICP in patients outwith infancy and in individual young infants. The RI was a reliable index for assessment and monitoring purposes. Volume-flow velocity response studies during CSF taps suggest there is an exponential relationship between RI and CSF volume drained. The sleep study results suggest that some patients are able to haemodynamically compensate during episodes of raised ICP while patients with a decreased MFV response may be at greater risk with inadequate haemodynamic compensation.

Patients with meningitis had increased RI associated with decreased EDV and MFV values during the early phase. CBFV values especially the RI was helpful for monitoring cerebral haemodynamic trends.

During CPB surgery MFV decreased significantly during hypothermic bypass perfusion, mainly associated with the fall in the systemic arterial

pressure. TCD monitoring was also very sensitive in the detection of cerebral microemboli signals. It may be a useful monitoring technique which can provide immediate and continuous feedback of cerebrohaemodynamic changes to surgeons, anaesthetists and perfusionists. It may also be helpful in the assessment of children with an acute stroke after surgery.

Chapter 1

INTRODUCTION - Aims and Objectives

In infancy and childhood fatal or seriously disabling brain damage can result from impaired cerebral perfusion in a number of clinical disorders. The brain is particularly sensitive to the effects of ischaemia and maintenance of a minimal critical level of perfusion is essential to prevent irreversible damage (Jones et al 1981, Trojaborg & Boysen 1973). Regulation of the cerebral circulation through different mechanisms will vary depending on the underlying disease state (Lassen 1974). With the improvement in prognosis for many serious childhood diseases, therapeutic intervention is now increasingly directed towards improving neurological outcome. The prevention of secondary ischaemic damage by maintaining an adequate cerebral blood flow, preventing intracranial hypertension and other poorly understood secondary cerebral insults has now become the focus of considerable interest. Thus the practical means of monitoring the intracranial and cerebrohaemodynamic trends in various clinical conditions is necessary towards gaining greater insight into the pathophysiology of brain insults and our search to develop improved treatment strategies to minimise neurological morbidity.

Raised intracranial pressure is an important contributing factor in the pathophysiology of cerebral injury from diseases such as hydrocephalus, meningitis, head injuries, encephalopathies, brain tumours etc. It causes two distinct pathological processes; a reduction of cerebral blood flow due to reduced cerebral perfusion pressure, or brain shifts and cones, resulting in secondary ischaemic damage or brain herniation. Primary ischaemic insult due to cerebrovascular thrombotic, haemorrhagic and hypotensive events may occur for example in distressed or preterm neonates, following head injury, during cardiopulmonary bypass surgery or in children with congenital abnormalities such as vascular malformations, vasculopathies, coagulopathies, etc.

There are now many methods available for measuring cerebral blood flow (Merrick 1991). Standard reference techniques such as flow meters, labelled microspheres and autoradiography can provide absolute

measurements of bloodflow but are usually used in experimental settings and are not clinically practical. Clinical methods of cerebral blood flow (CBF) measurement which have been developed include Doppler ultrasound techniques, magnetic resonance imaging (MRI), use of diffusible tracers such as $^{133}\text{Xenon}$ by the intra-arterial, intravenous or inhalational methods, tomographic methods such as stable Xenon - computerised tomography (CT) scans, single photon emission computed tomography (SPECT), positron emission tomography (PET), and first-pass methods. Each of these clinical methods offer separate advantages and limitations but all these methods require validation against one of the standard reference techniques.

Use of diffusible tracers, such as $^{133}\text{Xenon}$, for monitoring purposes is very much restricted by its limited repeatability especially in children, due to cumulative radioactive exposure. Recently, modification of the Kety-Schmidt technique using nitrous oxide in head-injured children has been described (Sharples et al 1991) but this technique remains invasive and can only be applied in the intensive care setting in comatose children. Magnetic resonance, PET and SPECT scanners are highly expensive equipment which are currently not yet widely available for clinical purposes. Another important limitation of these techniques for monitoring purposes is that the patient has to be brought to the equipment, so repeated measurements cannot be easily undertaken especially for ill or comatose patients. Scanning methods such as computerised tomography (CT), MRI and PET also require a considerable degree of patient cooperation to lie very still during what may be a lengthy procedure and this is usually not achievable in young children without some form of heavy sedation or general anaesthetic which also further limits repeatability.

Advantages of the transcranial Doppler ultrasound (TCD) technique are its relatively inexpensive cost, its easy application for bedside monitoring as the equipment is compact and portable, and it can be performed repeatedly in sick patients. These features together with its non-invasive nature render it an attractive and readily acceptable technique particularly for children. However, this technique also has a number of limitations

and it is thus important to elucidate these limitations and to clarify what inferences may reliably be drawn in various clinical settings.

Aims and objectives

The aim of this thesis will be to evaluate the role of transcranial Doppler ultrasound as a practical method of monitoring cerebral haemodynamic trends in children in clinical conditions where cerebral haemodynamic homeostasis may be altered. I applied the TCD technique to measure cerebral blood flow velocity (CBFV) indices specifically in four main study groups: (1) normal children without neurological disease (the control group), (2) infants and children with hydrocephalus, (3) infants and children admitted with pyogenic meningitis, and (4) children undergoing cardio-pulmonary bypass (CPB) surgery. The CBFV profile and cerebrohaemodynamic changes occurring in these conditions are assessed and the application and reliability of the various Doppler indices obtained are evaluated.

Chapter 2

DOPPLER ULTRASOUND

In 1843 Christian Doppler presented his paper on the effect of movement between the observer and emitting source on perceived light frequencies. He offered examples from astronomical observations which were in fact incorrect. However further experiments by other scientists in subsequent years including Buys Ballot and Belopsolski have added to the correction and clarification of the original observations. The Doppler principle, as accepted now, relates the shift in frequency of a wave when either the transmitter or the receiver are moving with respect to the wave propagating medium. This was applied to the measurement of flow velocity in blood vessels in 1961 (Franklin 1961) and since then Doppler ultrasound techniques have been widely applied in clinical practice with constantly improving instrumentation.

Doppler ultrasound techniques have considerable applications particularly in paediatrics as they are non-invasive, safe and easily repeatable without the use of radioactive isotopes. This was applied to the measurement of cerebral blood flow velocity (CBFV) by Bada et al in 1979 using the transfontanelle approach to study flow in the anterior cerebral arteries of neonatal patients after birth asphyxia and intraventricular haemorrhage. With the use of a lower frequency probe (2 MHz) for improved transmission through specific 'windows' such as the thin temporal squamous bone or selected cranial foramina, Transcranial Doppler ultrasound (TCD) techniques were described by Aaslid et al in 1982 for the measurement of intracranial arterial flow velocities. TCD techniques allow the measurement of basal CBFVs in all age groups except for approximately 5 - 15% of individuals where recordings from the temporal window are unsatisfactory due to increased skull thickness. TCD is less expensive, more commonly available, and more practical for bedside monitoring purposes compared to the newer techniques of measuring CBF such as stable Xenon - CT, MRI, SPECT and PET scans.

2.1 Doppler theory

The Doppler formula as applied to the measurement of blood flow velocity using ultrasound waves is:

$$df = 2 \cdot f \cdot v \cdot \cos \theta / c \quad \text{- Equation 1}$$

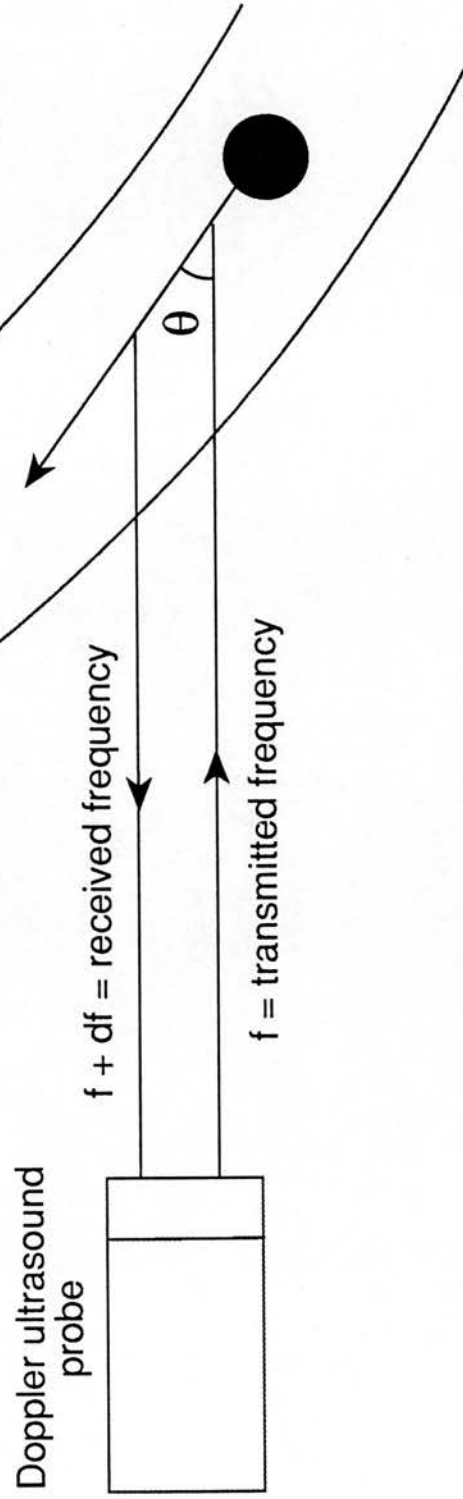
where: df = shift in frequency (difference between received and transmitted frequency),
 f = transmitted frequency,
 v = velocity of blood cells,
 θ = angle of insonation,
 c = velocity of ultrasound in soft body tissues (approx 1540 m/sec at 37° C).

An ultrasound beam directed at the vessel investigated is scattered by moving blood cells, primarily erythrocytes, and the shift in frequency of the backscattered beam allows calculation of the blood flow velocity according to equation 1 (Figure 2.1). The angle of insonation, θ , is the angle between the axis of the ultrasound beam and the direction of motion.

Individual erythrocytes act as point scatterers and the combined effect is referred to as the Rayleigh-Tyndall effect where the intensity of the scattered wave increases with the fourth power of the frequency. Thus doubling the ultrasonic frequency will result in a sixteen-fold increase in the intensity of the echo from blood cells. However, attenuation in soft tissue also increases with frequency thus offsetting the improved scattered intensity at higher frequencies. In the clinical setting the choice of the optimum frequency for the Doppler probe will be a compromise depending on the depth of the structure of interest and the intensity of the reflected signal. A working rule is that the optimum frequency f_{opt} (in MHz) for the examination of a structure separated from the transducer by d mm of soft tissue is given very approximately by the relationship: $f_{opt} = 90/d$ (Burns 1987). Another important effect is the interference pattern produced by the supposition of many individual scattered waves which causes fluctuations in the strength of the Doppler signal both in time and space. This may produce noisy signals with poor clarity of the spectral outline.

Figure 2.1:

$$\text{Doppler equation : } df = \frac{2 f v \cos \theta}{c}$$



v = velocity of blood cell
 θ = angle of insonation
 c = velocity of ultrasound in soft body tissue

2.2 Doppler systems: continuous- and pulsed- wave ultrasound

2.2.1 Continuous - wave

The simplest Doppler instrument is the continuous-wave Doppler detector which was first introduced about thirty years ago. The transducer has separate transmitting and receiving elements and is placed over the plane of the blood vessel's longitudinal axis. Ultrasonic waves are continuously transmitted in a narrow pencil beam and a continuous stream of echoes arrive at the receiving transducer; the difference in frequency between the transmitted and received ultrasound being the Doppler shift. All blood vessels in the path of the ultrasound beam contribute to the backscattered echo; consequently, although it may be possible to study a specific vessel by adjusting the transducer position, signals may be simultaneously received from more than one vessel and summated, leading to errors in data interpretation.

2.2.2 Pulsed- wave

Short bursts of ultrasound are transmitted at regular intervals from the same transducer which is also used for receiving the returning echoes. The repetition rate of these bursts is called the pulse repetition frequency (PRF). By changing the length of time the system waits after sending a pulse before opening the gate that allows it to receive echoes, the depth of tissue from where the signals are sampled can thus be adjusted (range gating). Specific vessels can then be insonated more reliably by changing the depth of sampling and the orientation of the beam.

An important consequence of the pulsed-Doppler system is the phenomenon of aliasing. In theory, unambiguous reconstruction from a sequence of samples is possible when the lower frequency limit of the signal is zero and the maximum frequency present is less than half the sampling rate (Nyquist limit). As ultrasound echoes have to return before the next burst is sent, the depth of insonation will impose a limit on the pulse repetition frequency. Thus on occasions when the frequency of the returned beam is above the Nyquist limit for that depth, for example when sampling from spastic vessels, an incorrect or 'aliased' shift frequency due to a 'fold-over' of the high frequency components causes ambiguity in the spectral display. Measures to overcome 'aliasing'

include increasing the pulse repetition rate, lowering the ultrasound frequency or changing to a continuous-wave mode which is not affected by the aliasing limitation. Pulsed Doppler instruments, especially for transcranial applications, usually have a poorer signal-to-noise ratio than continuous -wave systems and this is commonly addressed by increasing the power of the transmitted pulse.

Greisen et al (1984) have shown from neonatal studies that in comparison with cerebral blood flow measured by the intravenous $^{133}\text{Xenon}$ clearance method there was consistently higher correlation for the Doppler ultrasound variables obtained by the range-gated, pulsed-wave technique than by the continuous-wave technique. For transcranial applications, essentially a 'blind' technique, the continuous-wave Doppler technique has no role as it would be unable to discriminate the specific vessels in which velocity changes occur and thus would be very unreliable.

2.3 Doppler ultrasound machines: transcranial Doppler, duplex and colour flow mapping

2.3.1 Transcranial Doppler (TCD) ultrasound scanners generally use a directional pulsed-wave probe which records range-gated Doppler measurements at selected depths inside the skull. The intracranial vessels are not directly visualised and identification depends on the depth of the sample volume, angulation of the probe, the relationship to the internal carotid artery bifurcation and specific flow characteristics such as the direction of flow (towards or away from the transducer) and the spectral pattern. TCD examination techniques are well described (Aaslid 1986, Fujioka & Douville 1992). The transtemporal window allows examination of the middle cerebral artery (MCA), proximal anterior cerebral artery, proximal posterior cerebral artery, and the distal internal carotid artery (ICA). The transforaminal window (through the foramen magnum) can be used to examine the vertebrobasilar circulation, and the transorbital window can be used to insonate the ophthalmic artery and the carotid siphon. A flow mapping technique which reconstructs a computerised map of the vasculature from three dimensional coordinates has been developed to facilitate vessel identification (Aaslid 1986).

2.3.2 Duplex scanners combine B-scan imaging with pulsed-Doppler techniques. These scanners are very useful for the study of cerebrovascular flow velocity in neonates and infants with unfused anterior fontanelles. Real-time imaging is used to select the specific location for interrogation with the Doppler system thus allowing more accurate identification of a specific vessel. Another advantage of the duplex system is that the angle of insonation can be estimated and hence the true velocity of flow may be more reliably obtained. Volume flow estimations may also be attempted if the vessel area can be estimated as volume flow = mean velocity \times cross-sectional area (πr^2). However, the margin of error will be enormous when attempting to estimate the cross-sectional area of intracranial vessels particularly in young infants.

2.3.3 Colour-flow mapping which presents superimposed colour-coded blood flow information on a grey-scale B-scan image is a useful addition to duplex scanning systems. Colour flow imaging for TCD has been a recent advance to help in vessel identification (Bogdahn et al 1990) and normal values of angle-corrected "true" flow velocities in basal cerebral arteries from transcranial colour duplex sonography techniques have been reported in childhood and adolescence recently (Schoning et al 1993).

2.4 Analysis of Doppler frequencies

Accurate analysis of Doppler information depends on the method of processing the data. The blood cells within the sample volume will be moving at a range of velocities, occasionally even in opposite directions throughout each cardiac cycle. The zero crossing detector method of assessing the mean of the frequency spectrum at each instant throughout the cardiac cycle was widely used in earlier reports on neonatal patients. With this method the presence of noise, simultaneous forward and reverse flow, and signals from more than one vessel are all liable to introduce serious errors (Lunt 1975).

Most modern Doppler instruments use a frequency (or spectrum) analyser to process the combination of different Doppler shift frequencies contained within the signal. Short periods of the signal are analysed by the Doppler unit and the magnitude of each frequency component is estimated. A

series of spectra is produced which scrolls from left to right in real time with the frequency component displayed on a vertical scale and a grey scale representing the signal intensity at a given frequency. This form of display is referred to as a spectrogram (Figure 2. 2). A better spectral display can usually be obtained by performing and averaging many analyses to reduce the random fluctuations of the spectral amplitudes. This also reduces the background noise which is important when tracing the spectral outline. The quality of the sonagram and the audio signal obtained in real time helps the clinical operator to obtain optimal probe position.

2.4.1 Effect of Insonation angle:

The velocity component causing the frequency shift can be derived from the Doppler formula accordingly depending on the transmitted frequency: $v = 39 f$ (for 2 MHz probe), $v = 19.5 f$ (for 4 MHz probe); v in cm/sec, f in kHz. It must however be kept in mind that calculation of these measures are dependent on the angle of insonation, the relationship between the true velocity (v_t), the observed velocity (v_o) and the insonation angle (θ) being: $v_o = v_t \cos \theta$.

The percentage error in velocity estimation increases rapidly with increasing angles of insonation as shown in Figure 2.3. When θ is not zero, the percentage error is $[(v_t - v_o) / v_t] \times 100 = (1 - \cos \theta) \times 100$. Within an insonation angle between -30 to +30 degrees, the observed velocity is within 0 and 13% of the true velocity while there is greatly significant error (> 50%) at insonation angles above 60°. In transcranial applications the strait-jacket imposed by a small ultrasonic window tends to minimise the error caused by different operator techniques. In particular, it is suggested that for normal individuals the temporal window allows almost zero insonation angle for the middle cerebral artery. However while this may be the case when the cerebrovascular anatomy is relatively normal, this cannot be reliably assumed in conditions such as hydrocephalus where the course of the intracranial vessels may be significantly distorted and stretched by ventricular dilatation (Finn et al 1990).

2.4.2 Waveform analysis

Under conditions of laminar flow, the flow profile in major cerebral arteries such as the MCA, in the absence of turbulence or excessive arterial branching, is assumed to be parabolic. The maximum flow velocity thus occurs at the centre of the vessel and is reflected as the maximum outline of the spectral tracing. The minimum flow velocity will occur near the wall of the artery. As the entire cross-section and a relatively large segment of the cerebral artery may be within the sample volume, each moving part of the the blood within the sample volume will contribute to a mixture of Doppler shifts consisting of many frequencies with different signal intensities. Information contained in a spectrogram is thus rather complex and it is necessary to extract more simple information from it to quantify for analysis.

2.4.2.1 Mean Flow Velocity (MFV)

In most TCD instrument design the maximum velocity envelope (i.e. the envelope or spectral outline velocity) is used for analysis. The peak systolic velocity (PSV) is the maximum flow velocity noted in systole during left ventricular contraction and the end diastolic velocity (EDV) is the maximum velocity noted just prior to the acceleration phase of systole (Figure 2.4). The mean flow velocity (MFV) is usually obtained from the time-averaged maximum velocity (averaged over the cardiac cycle); this is calculated automatically by many current TCD instruments and is most frequently used by the majority of authors. Although it is theoretically possible to calculate the mean velocity by weighted averaging of each component of the Doppler spectrum, this approach is only valid under a number of conditions which are usually not met in typical clinical situations. In conditions of laminar parabolic steady state flow there is a constant relationship between the the maximal velocity and the mean velocity. This condition has also been shown to hold in neonatal cerebral arteries (Evans 1985). Built-in electronic calipers or cursors are generally used to make measurements such as the peak-systolic and end-diastolic frequencies from the spectrograms.

If relying on automatic quantification of the MFV, the utmost care in adjusting the gain and acquiring an entire series of high quality spectral waveforms is always required. Values obtained from spectra with a low

signal-to-noise ratio will be highly inaccurate and unreliable and manual or hand calculations of the MFV may be required if automatic computation is invalid. Lindegaard (1992) has shown that from the same raw data the automatically computed outline MFV was more susceptible to change with gain variation compared to the manually obtained MFV.

Increase in MFV may represent an increase in mean volume flow if the vessel diameter remains constant although conversely an increased MFV may also be due to vessel narrowing at the site of measurements. Chan et al (1992) have suggested from data in severely brain-injured patients that the presence of a diastolic notch in the MCA velocity waveform of those with increased MFV values may indicate vasospasm, while in those who did not show a diastolic notch the increased MFV values were indicative of hyperaemia due to vasodilatation.

2.4.2.2 Indices of pulsatility

The shape of the Doppler waveform is also of clinical interest because the pulsatility of the waveform is influenced, amongst other factors, by the impedance of the distal vascular bed. Pulsatility analysis examines the degree of variability in the maximal flow velocities that occurs during the different phases of the cardiac cycle as a result of the pulsatile nature of the heart pump. In a defined artery the shape of the waveform results from the interaction of two variables i.e. the input signal and the organ related factors. Because of their simplicity, a number of indices which are varying ratios of peak-systolic, end-diastolic and mean velocities have been widely used in clinical studies. The end-diastolic velocity is likely to be most influenced by the distal/peripheral vascular resistance of the end-organ. As these indices are ratios an important theoretical advantage is that they are not dependent on the angle of insonation because this factor is present in the numerator and denominator and thus cancelled out. However Winkler and Helmke (1990) have reported that with stepwise increments in the angle of insonation, the diastolic frequency was reduced to a greater extent than was the systolic frequency and thus the pulsatility indices obtained at large insonation angles may be inaccurate.

2.4.2.2 (i) The Gosling Pulsatility Index (PI)

The Gosling Pulsatility Index was initially applied to the study of blood flow velocity waveforms in peripheral arterial disease and was originally defined as the sum of energies in the first and subsequent Fourier harmonics of a velocity waveform, divided by the energy in the zeroth harmonic (Gosling et al 1971). This was later simplified as the Pulsatility Index (PI) which is the ratio of the peak-systolic minus the end-diastolic velocity divided by the mean flow velocity i.e. $PI = (PSV - EDV)/MFV$. The calculation of MFV introduces an additional third source of potential error and reduces the reproducibility. It is important to appreciate that automatic calculation of the PI may be unreliable if poor quality, noisy spectra are obtained, reducing the accuracy of MFV measurement. However, the PI is automatically computed by a number of commercially available TCD ultrasound systems and it is now quite widely reported in the literature. It is thus essential that for automatic analysis there is rigorous selection of good quality data.

2.4.2.2 (ii) The Pourcelot Resistance Index (RI)

The Pourcelot Resistance Index, RI, was introduced by Planiel and Pourcelot (Pourcelot 1976) to detect abnormalities in distal cerebrovascular impedance in the territory perfused from the common carotid artery. The RI is the ratio of the peak systolic velocity minus the end-diastolic velocity divided by the peak systolic velocity; $RI = (PSV - EDV)/PSV$. The maximum value of RI is thus 1. Since it was first applied by Bada et al in 1979 to examine flow velocity in the anterior cerebral artery, the RI has been widely reported in the neonatal literature in particular.

In some literature the Pourcelot Resistance Index has occasionally been abbreviated to PI and has been confused with the Gosling Pulsatility Index. Although both indices essentially provide a measure of the variability in the waveform shape over a cardiac cycle, it is important to avoid such errors as they differ numerically and each component of these indices may be variably affected by changes in distal impedance, pump forces or cerebrovascular compliance. Unlike the RI, the PI is influenced also by the late systolic and early diastolic components of the waveform. Correlation analysis of the PI and the RI shows a linear relationship; however there is not an exact fit and a given RI may correspond to a range

of PI values. It is thus important to clarify which index has been used as well as to analyse which component of the waveform contributed most significantly to observed changes in pulsatility.

2. 4. 2. 2 (iii) The S/D ratio (S/D)

This is the ratio of the peak systolic to the end-diastolic velocity and has mainly been used in obstetric work to study the placental circulation. Note however that as diastolic velocity approaches zero, S/D becomes infinite.

Pulsatility can be influenced by input as well as distal factors resulting from physiological changes, cardiac status and some pathological states. The input signal from the systemic blood pressure waveform has an important influence on the pulsatility of the cerebral arterial waveform. One example is the uniform non-pulsatile flow seen in recordings during non-pulsatile cardiopulmonary bypass surgery (Lundar et al 1985) when the blood pressure is 'driven' by the non-pulsatile pump. Another example is in infants with patent ductus arteriosus who have low diastolic blood pressure, the CBFV waveforms also show increased pulsatility (Snider 1985) and can superficially resemble the flow reverberations occurring in brain tamponade (Hassler et al 1988, Bode 1988).

In experimental flow models, *in vitro* pulsatility has been shown to be positively correlated with peripheral resistance (Legarth & Thorup 1989). However in clinical settings, low pulsatility and high velocities have been associated both with a decrease in downstream resistance such as in arteries feeding arterio-venous malformations and also seen distal to a vessel stenosis or occlusion (Lindegaard et al 1986, Giller et al 1990). Giller et al showed that the drop in pulsatility associated with a given increase in velocity was significantly greater when the velocity increase was due to diminished downstream resistance (patients with arteriovenous malformations) than from stenosis (aneurysmal vasospasm).

Other more sophisticated methods of analysing the Doppler waveform include principal component analysis (Evans et al 1985) and the application of Fourier analysis to the velocity waveforms (Aaslid et al

1986). These more sophisticated methods of waveform analysis may help to improve the accuracy of transcranial Doppler recordings for estimation of perfusion pressure or impedance compared to the conventional, more simplistic approaches described. However the addition of linked computer processors will be required to perform these analyses and further work is still needed before these systems are validated and widely available for clinical studies.

Figure 2.2: Spectrogram of Doppler velocity waveforms produced from the Doptek Decoder ultrasound machine. The vertical scale represents the frequency component (kHz) and the horizontal scale represents time.

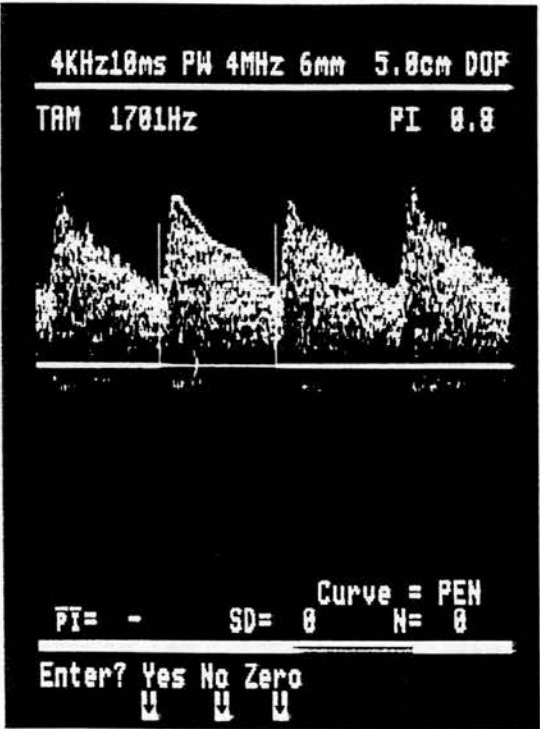


Figure 2.3 shows percentage error in measured velocity with increasing angle of insonation

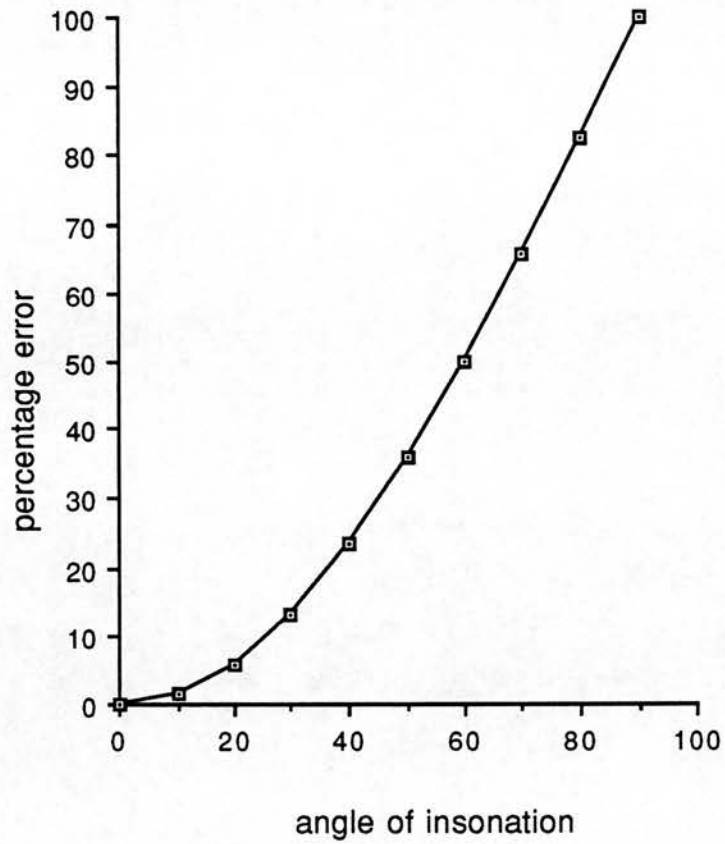
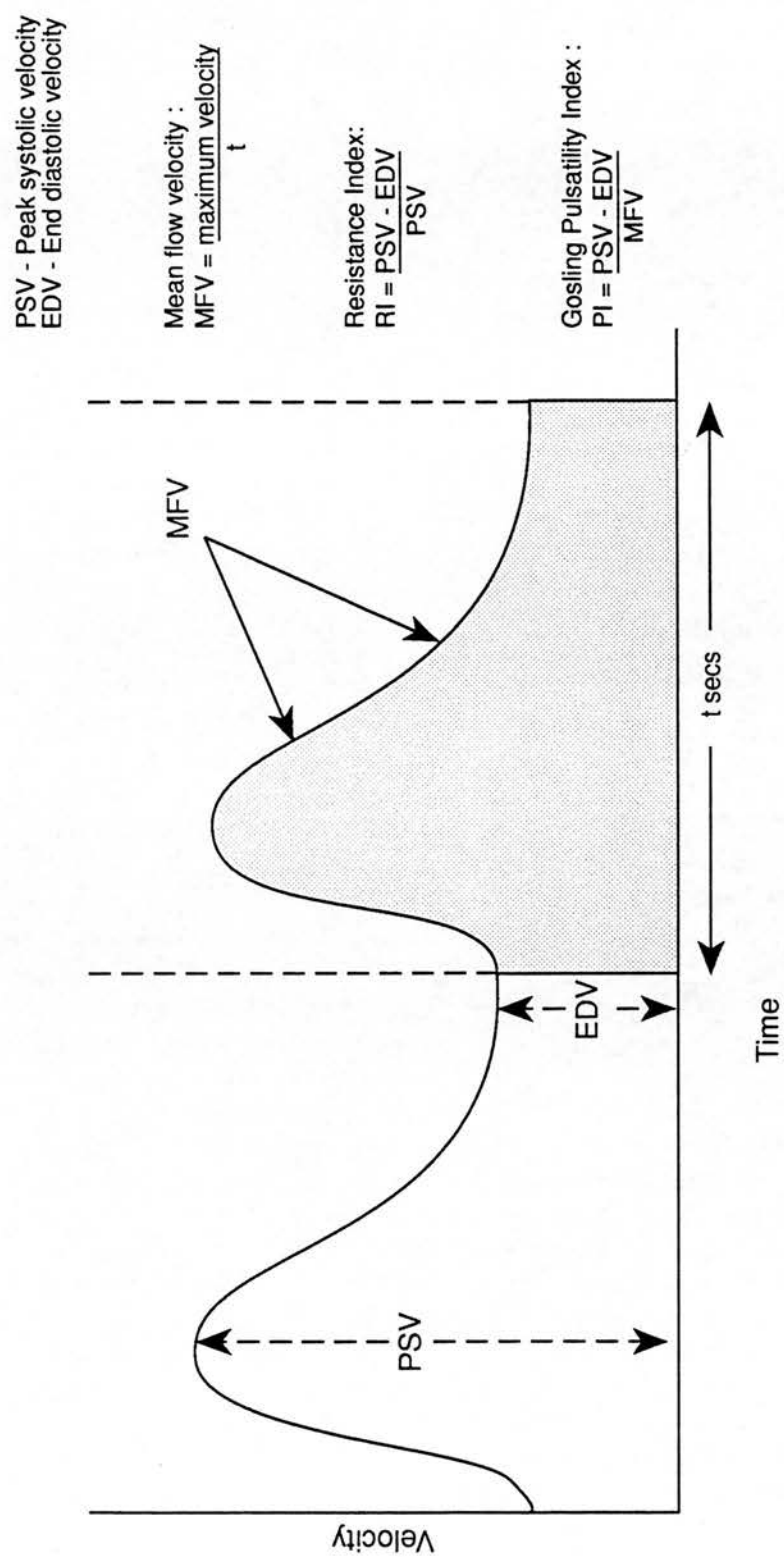


Figure 2.4 Diagram of Doppler waveform - peak systolic, end-diastolic, mean flow velocity



2.4.3 Reproducibility and sources of error

2.4.3 (i) Size of ultrasonic window

The most important factor influencing reproducibility is likely to be the size of the ultrasonic window which determines the stability of the angle of insonation. The temporal bone provides only a small ultrasonic window in comparison to the foramen magnum (for the basilar/posterior cerebral arteries) or the anterior fontanelle in very young infants (for the anterior cerebral artery) where the larger windows allow detection of flow velocity signals from highly variable angles. Both the inter- and intra-observer reproducibility of TCD measurement are reported to be much better for the MCA compared to the basilar artery (Maeda et al 1990).

2.4.3 (ii) Effect of gain variation

Lindegaard (1992) assessed the effect of variation in signal intensity on analysis of raw data obtained from the MCAs bilaterally in 10 patients and showed that the intensity of the spectral display is an important and potentially confounding variable in TCD measurements. Higher velocity values are obtained when the gain is increased while decreasing the gain yields lower values when compared to values obtained from the best screen display. The diastolic velocity was the most sensitive variable, probably because the diastolic velocity is lower. The value of pulsatility indices tend to increase with decreasing gain as the effect on diastolic frequencies is greater. However at very low settings when reading the systolic frequency becomes difficult too, pulsatility values could drop markedly. The Pourcelot RI showed qualitatively similar observations but with less pronounced variation from the values obtained from the best screen compared to the Gosling PI.

2.4.3 (iii) Manual versus automatic computation

The automatically computed outline MFV performed much like the manually obtained MFV but was more susceptible to change in gain variation (Lindegaard 1992). The human eye is very good at distinguishing background spectral noise and artefacts from genuine signals. It is clear that optimal signals with good signal-to-noise ratio are essential for reliable automatically computed values. However, manual analysis of continuous recordings is very time-consuming and results

quoted by most authors are usually from automatically computed data. The computer is also unable to distinguish between changes in the Doppler data which reflect true changes in blood velocity and those alterations which may follow probe displacement or gain manipulation during the period of data acquisition. Thus critical selection of data for recording and analysis is also required; hence an experienced operator is usually required to be present throughout the majority of the duration of Doppler data acquisition.

2.4.3 (iv) Intra- and inter- observer variability

Maeda et al (1990) reported an intraobserver coefficient of variation of 7.5% for measurement of the MFV for two investigators on one day and of 13.2% on separate days (mean interval 22 days). The inter-observer coefficient of variation on the same day was 10.5 %. Sorteberg et al (1990) reported similar intraobserver variability of 9% for examinations a day apart and 12% over a 7 day interval.

2.4.3 (v) Quality and adjustment of Doppler instruments

Noise, crosstalk or signals from wall movement may imitate flow velocity signals. However, high-pass filters designed to cut off such low frequencies may cause difficulty in the investigation of low flow velocities. No signal can thus be erroneously taken to equal no flow or the mean velocity may be overestimated due to cut-off of low velocities. Low sensitivity or signal-to-noise ratio of the Doppler instruments, with inadequate precision or inappropriate wall filter settings can significantly affect results. There may also be inadequate separation of two closely adjacent vessels having the same direction of flow.

2.4.3 (vi) Examination technique

A relatively large angle of insonation ($> 30^\circ$) will significantly affect the estimation of the flow velocities. In particular values of absolute flow velocities, i.e. the MFV, PSV, and EDV will be more significantly affected than the values of pulsatility indices. However at large angles of insonation even these indices obtained may be misleading, as previously discussed.

2.4.3 (vii) Interpretation

Whilst there is currently an intense level of clinical research activity utilising this technique in a wide number of physiological and pathological conditions affecting the cerebral circulation, interpretation of cerebral Doppler flow velocity changes remain a matter of considerable controversy. A characteristic flow velocity spectrum can be the result of a number of diverse physiological and pathological conditions. The RI or PI may be influenced by many other factors apart from the peripheral resistance such as the arterial blood pressure, vessel elasticity, transmural pressure, heart rate, blood viscosity and flow profile. It is also simplistic to assume that changes seen in one cerebral artery may be taken to represent changes in the entire cerebral circulation. Examination of other cerebral arteries and of the cerebral venous system may be required to clarify the haemodynamics in various conditions. Reliable interpretation depends very much on obtaining other concomitant measurements such as intracranial pressure, cerebral perfusion pressure, mean arterial pressure in support of the conclusions drawn. Thus interpretation of changes seen in one clinical setting needs to be carefully qualified and conclusions derived from one set of clinical conditions cannot necessarily be reliably extended to other settings.

2.4.4 Measurement of volume flow

If the cross-sectional diameter of the vessel can be measured accurately, the mean volume flow can theoretically be estimated from the product of the cross-sectional area of the vessel lumen and the mean flow velocity. This has been attempted for larger arteries using duplex ultrasound when the vessel angle can also be estimated but is currently unavailable for cerebral arterial measurements in older children and adults and highly unlikely to be reliable in young infants. If however the area of the vessel lumen can be assumed to remain constant, changes in mean flow velocity may serve as a reliable guide to *relative changes* in mean volume flow and this has been demonstrated in in-vitro studies (Lundell et al 1984). Changes in cerebrovascular resistance are generally thought to be mediated through changes in peripheral vascular tone at the arteriolar level, rather than in the major cerebral arteries themselves. Changes of arterial carbon dioxide partial pressure (pCO₂) for example, cause considerable changes in cerebral blood flow, mainly through altering peripheral vascular resistance.

Huber and Handa (1967) showed from angiographic studies that there was little change in the diameter of the large arteries with changing serum carbon dioxide tension. Blood flow velocity in the MCA from transcranial Doppler studies has been shown to be dependant on $p\text{CO}_2$ changes (Markwalder et al 1984, Kirkham et al 1986) in a similar relationship to changes in cerebral blood flow reported from xenon clearance methods of measurement .

However, there remains considerable controversy on whether there can be significant change in the diameter of large cerebral arteries from which Doppler measurements are obtained. Recent research has suggested that the diameter of a large artery changes in response to local haemodynamic forces, haematocrit, and arterial carbon dioxide pressure (Brant et al 1987, Melkumyants et al 1989, Faraci et al 1987) and that up to one-third of the total cerebral vascular resistance can be attributed to cerebral arteries greater than 150 μm diameter (Faraci et al 1987). As volume flow is related to the fourth power of diameter (Poiseuille's law) even minor changes in the arterial diameter can produce significant changes in the volume flow.

2.5 Validation studies

2.5.1 In-vitro studies:

In an in-vitro pulsatile flow model, Lundell et al (1984) using the pulsed - Doppler technique found the MFV to be the most reliable estimate of true flow. There was a negative but curvilinear relationship between the Pourcelot RI and increasing flow. Using continuous-wave Doppler, Miles et al (1987) reported highly reliable correlations of all Doppler measures, including the Pourcelot RI and Gosling PI, with volume flow rate when the probe angle remained constant in their in-vitro study. In a cardiovascular in-vitro model consisting of a heart simulator and a circulatory tube system, Legarth and Thorup (1989) have shown that the PI was a flow- and pressure- independent estimate of peripheral resistance.

2.5.2 Animal studies:

Earlier validation studies in animal models have been performed using continuous-wave bidirectional Doppler velocimeters from a

transfontanelle approach to study CBFV. A study by Hansen et al (1983) comparing Doppler flow velocity and brain blood flow using the microsphere method in piglets found a significant positive relationship for PSV, EDV and MFV while there was no correlation for the Pourcelot RI. Batton et al (1983) obtained similar results in newborn puppies when Doppler velocities were compared with regional CBF determined by C¹⁴ iodoantipyrine autoradiography; their results suggested that the RI was indirectly and not directly related to cerebral vascular resistance. It is important to bear in mind that results from these early experimental and clinical studies were obtained using less sophisticated technology and analysis, such as the zero-crossing detector method, and thus may not be as reliable as results obtained from validation studies carried out in more recent years.

In a more recent study, by manipulating ICP via cisterna magna infusion in a rabbit model, Barzo et al (1991) have also shown that in the lower range of autoregulation, i.e. at perfusion pressure between 80 and 40 mmHg, the changes in blood flow velocity from the internal carotid artery (ICA) and cerebral blood flow measured by the hydrogen clearance method showed a strong correlation ($r = 0.86$) under conditions of standard pCO₂.

2.5.3 Clinical studies:

In normal newborn infants Greisen et al (1984) compared pulsed and continuous-wave ultrasound velocity measures from the anterior cerebral and internal carotid arteries with CBF obtained from intravascular ¹³³Xenon clearance. There was a consistently higher correlation for MFV and EDV than for the RI.

Bishop et al (1985) found that percentage changes in MFV in response to pCO₂ changes in normal adults correlated reliably with changes in CBF measured by intravenous ¹³³Xenon although correlation for absolute levels were unreliable due to wide interpatient variation. Lindegaard et al (1987) compared flow velocity in the MCA with volume flow in the ipsilateral ICA measured with an electromagnetic flowmeter during periods of transient rapid blood flow variations in 7 patients after carotid endarterectomy or during non-pulsatile cardiopulmonary bypass. They found a very close correlation between these two measures for each

patient. Sorteberg et al (1989) reported a reliable correlation for the MCA ($r = 0.63$, $p < 0.001$) and posterior cerebral artery ($r = 0.73$, $p < 0.001$) flow velocities, when normalised to a standard $p\text{CO}_2$ using accepted formulas, and regional cerebral blood flow (rCBF) data in normal adults, obtained from $^{133}\text{Xenon}$ inhalation and dynamic techniques. Brass et al (1987) also reported a close correlation when comparing velocity changes in the MCA with $^{133}\text{Xenon}$ rCBF in clinically stable patients with sickle cell anaemia. During cardiac operations, van der Linden et al (1991) have shown a highly significant correlation between MCA flow velocity changes and thermodilution-estimated blood flow changes from the ipsilateral internal jugular vein (overall correlation 0.77, $p < 0.001$).

The consensus of results from these validation studies are that changes in the mean velocity can closely reflect changes in cerebral blood flow assuming that during the conditions of measurement there are unlikely to be significant changes in cerebral arterial diameter or in the angle of insonation. Change in the waveform pulsatility does not directly reflect blood flow volume change. However it could be a useful index of cerebral perfusion pressure or cerebrovascular resistance variation in certain clinical situations.

2.6 Relationship of waveform pulsatility to intracranial pressure and cerebrovascular resistance.

Characteristically increased pulsatility of Doppler waveforms have been reported in conditions with markedly raised intracranial pressure (ICP) leading to intracranial circulatory arrest (Hassler et al 1988, Bode et al 1988). As ICP increases, cerebral perfusion pressure (CPP) decreases and pulsatility increases with a marked progressive reduction in diastolic velocity which approaches zero when brain tamponade occurs as ICP becomes greater than the diastolic blood pressure. In comatose adults Klingelhofer (1988) and his colleagues found a positive correlation between increasing ICP and RI while MFV decreased correspondingly. Chan (1992) and his colleagues have shown that as CPP levels decreased below a critical value of 70 mmHg, there was a progressive increase in the Gosling PI which was consistent whether the decrease in CPP was due to an increase in ICP or decrease in MAP. This decrease in PI was due to the diastolic

velocity falling more than the systolic velocity. Experimental data in dogs (Seibert et al, 1989) have also shown a significant relationship between increased RI with decreasing CPP due to increased ICP.

In normal newborn infants Archer et al (1986) showed that the RI fell consistently with increasing end-tidal carbon dioxide concentration. This fall in RI was due to a rise in EDV, thus supporting the view that the RI correlates with cerebral vascular resistance distal to the site of recording as increased CO₂ tension is known to cause peripheral vasodilatation. In patients with vasospasm following subarachnoid haemorrhage Klingelhofer and colleagues (1991) found that an increase in RI values above 0.6 with a simultaneously decreased MFV indicated a rise in ICP rather than a reduction in vasospasm. In their patients changes in the MFV more reliably reflected the severity of vasospasm only in those with RI values of less than 0.5.

Evaluation of waveform pulsatility changes is thus more meaningful when simultaneous measurements of MFV and EDV are carried out. In some clinical conditions the pulsatility may serve as a reliable guide to changes in distal cerebrovascular resistance especially when the pulsatility changes can be related to changes in EDV.

2.7 Safety aspects of diagnostic ultrasound

Over the recent years, there have been many reports describing the biological effects of ultrasound both *in vivo* and *in vitro*. The suggested most likely mediators of bioeffects are heating which is related to power, and mechanical processes such as cavitation which may be influenced by factors such as pressure amplitude. It is unknown if either of these effects are cumulative over many scans although it is likely that factors such as temporal exposure would determine the temperature rise. These safety issues raised have been considered by a Working Group convened by the British Institute of Radiology which studied the available literature relating to the safety of diagnostic ultrasound and the group's conclusions have been published (Wells 1987). Their report concludes that there are no confirmed adverse effects of diagnostic ultrasound *in vivo* although it stresses that this should not permit complacency. The British Medical

Ultrasound Society has endorsed the American Institute of Ultrasound in Medicine's recommendation for spatial peak intensity averaged over time values of instruments used should be less than 100 mW/cm². As temporal exposure may be cumulative, it is also recommended that scanning time should be kept to the minimum duration required, with particular reference to the scanning of fetuses and neonates. With TCD, the estimated mean value of power loss through the skull is 80 %.

2.8 Clinical applications of Transcranial Doppler

As a non-invasive technique which is readily available for bedside measurement, TCD has become widely applied for evaluation of cerebrohaemodynamic changes in many clinical conditions. It has been recognised to be of established value in detecting severe stenosis in the major basal intracranial vessels, assessing the patterns of collateral circulation in patients with known regions of severe stenosis or occlusion, evaluating and following patients with vasoconstriction of any cause particularly after subarachnoid haemorrhage, detecting arteriovenous malformations and studying their major supply arteries and flow patterns and assessing intracranial velocity and flow changes in patients with suspected brain death (Caplan et al 1990). However currently there is intensive research activity in evaluating its role in further clinical applications. It has been reported to be helpful after severe head injury in the identification of reduced cerebral perfusion pressure states (Chan et al, J Neuro Surg 1992) and in the assessment of autoregulation and CO₂ reactivity for prognostic and therapeutic purposes in comatose patients with traumatic and non-traumatic encephalopathy (Lundar et al 1990, Kirkham 1991, Newell et al 1992). TCD has also been useful for the detection of emboli during cardiopulmonary bypass and endarterectomy operations (Padayachee et al 1987, Spencer et al 1990, van der Linden & Casimir-Ahn 1991), cerebral angiography (Markus et al 1993), and in assessing patency and pharmacologic responses of cerebral arteries after acute ischaemic stroke (Kaps et al 1990, Ley-Pozo & Ringelstein 1990, Karnik et al 1992). The value of TCD for evaluation and monitoring of infants and children with hydrocephalus is also being actively investigated.

There remains however considerable controversy regarding the interpretation of TCD data and more work is required in assessing its role as a means of studying cerebrohaemodynamic changes in children in conditions when cerebral perfusion may be compromised. What is also required is clarification of the value as well as the limitations of the specific Doppler indices and measurements made in each situation.

Chapter 3

METHODOLOGY AND PATIENT GROUPS

Methodology

3.1 Transcranial Doppler Ultrasound equipment and examination technique

Transcranial Doppler ultrasound signals were obtained using a 2 or 4 MHz pulsed-wave probe attached to a portable Doppler unit (Decoder, Doptek Ltd, Chichester, U.K.). The Decoder performs real-time spectral analysis on the ultrasound signal and displays a spectrogram with 64 grey levels in time increments of 5, 10, 20 or 40 milliseconds. The Doppler high pass filter level was always set at 100 Hz. With the Doppler unit set to deliver maximum power the spatial peak temporal average intensity of the beam was between 80 and 100mW cm⁻², measured using a calibrated bilaminar membrane hydrophone. At every examination due care was taken to use the minimum power required to obtain a satisfactory image. Safety checks on the ultrasound power were carried out by a medical physicist to confirm that the transmitted energy levels were within the guidelines recommended for prudent use of investigative ultrasound (Dubbins et al 1988, Wells 1987). The 2 MHz transcranial probe was specially modified, producing a flat button-shaped transducer of 16mm diameter and 10mm depth with a lightweight connecting cable thus allowing easy placement and good contact against the temporal bone. The 4 MHz probe was a cylindrical shape of 10mm diameter and 100mm in length. The minimum depth of insonation was limited, by the software of the Doppler unit, to 30mm for the 2 MHz probe and 20mm for the 4 MHz probe. In practice the 4 Mhz probe was only used in studying neonatal patients where the optimum depth of insonation for the MCA could be less than 30mm. Beyond the age of 2 - 3 months there was usually inadequate ultrasound penetration with the 4 MHz probe. Continuous and pulsed wave modes was available on the Doptek Decoder. However all recordings were carried out using the pulsed-wave mode. Occasionally the continuous-wave mode was helpful in finding the optimal temporal window.

Visual and auditory signals in real-time were obtained, with forward and reverse flow indicated by waveform spectra above and below zero frequency. With experience, the specific auditory characteristics of flow in the vessel of interest can be quickly distinguished aiding its detection and identification. All the Doppler data reported were taken from measurements in the MCA. Listening to the audible Doppler signal was particularly helpful in the initial part of every TCD examination. The real-time spectrogram allows immediate assessment of the quality of the signal, thus the best position and angulation of the probe can be quickly determined to enable recordings of optimal quality with minimal noise and interference. An overall gain control adjusts the displayed signal intensity, so that with a very noisy signal the gain can be reduced to remove background noise and interference or increased to enhance the waveform clarity of a poor signal. The range gate can be set to 2, 6 or 10mm length and its position can be adjusted in increments of 2, 3, 5 or 10mm.

When optimal signals were obtained, forward and reverse flow Doppler signals were recorded on the two channels of a high quality audio cassette deck (Yamaha KX500). A remote control box attached to the cassette deck allowed recording to be started or stopped, as well as voice dubbing of patient, physiological information and other simultaneous measurements onto the 'reverse' channel of the audio tape. The Doppler unit and the audio cassette deck were mounted together on a trolley which enabled it to be easily moved about for portable bedside measurements. Figure 3.1 shows the Doppler unit, the audio cassette deck with its remote control box mounted on a trolley; and Figure 3.2 shows the 2 and 4 MHz probes used.

When there was good patient cooperation, Doppler signals were generally recorded continuously for at least one minute for both serial and 'single' studies. Recorded Doppler signals were subsequently played back and analysed. There were four available scrolling speeds for the visual Doppler spectra on the screen at 5, 10, 20 or 40msec allowing closer inspection of waveforms if required. The peak systolic and end-diastolic frequencies and the outline of the maximum velocity envelope were traced by hand using a light pen and the RI of each single waveform as well as the time-averaged maximal velocity (MFV) were calculated by

software in the Decoder. Stable consecutive waveforms of the best quality were selected for analysis, the mean value then calculated from a minimum of 10 waveforms. This method allows accurate measurements to be made; as the selection was visual and tracing of data was done by hand, background noise in the spectrogram could be ignored as could waveforms distorted by patient or probe movement. The selection of waveforms for analysis was critical and data of poor signal quality or which were highly variable due to physiological events such as crying and coughing were not analysed. The values obtained from the Doppler unit are expressed in kHz, thus further conversion to velocity values in cm/sec was required.

3.1.2 TCD examination technique

Doppler examinations were performed with patients in a recumbent position when quiet or asleep, except for the normal controls who were mostly in a sitting position. A few patients were monitored in intensive care when they were on ventilatory support, usually in a sedated state. In the cardiopulmonary bypass study, patients were fully anaesthetised. Data obtained when patients were restless or upset were either not recorded or subsequently discarded as movement and noise caused great fluctuation in the signals obtained and the quality and reliability of the signals obtained were poor. In all studies the flow velocities in the MCA was measured as this vessel is most easily and reliably insonated at a constant angle from the temporal position.

The TCD examination begins with a search for the best position of the temporal window in each patient. This is located above the zygomatic arch and is usually a small defined area varying from just anterior to the external auditory meatus to the frontal process of the zygomatic bone (the posterior, medial and anterior temporal window). The pulsed-wave mode is first selected on the Doptek Decoder. The most likely optimal depth of insonation for the MCA was selected depending on the age of the patient, most commonly between 40 - 50mm; in the neonatal patients usually between 25 - 30mm (Bode & Wais 1988). Ultrasonic coupling gel to ensure good ultrasonic contact is applied to the probe and the skin, the probe is moved slowly in small steps anteriorly from the edge of the pinna towards the lateral margin of the eye continuously scanning for signals.

The MCA is normally the only artery with forward (or positive) flow seen between the depths of 25 to 50mm from the temporal window.

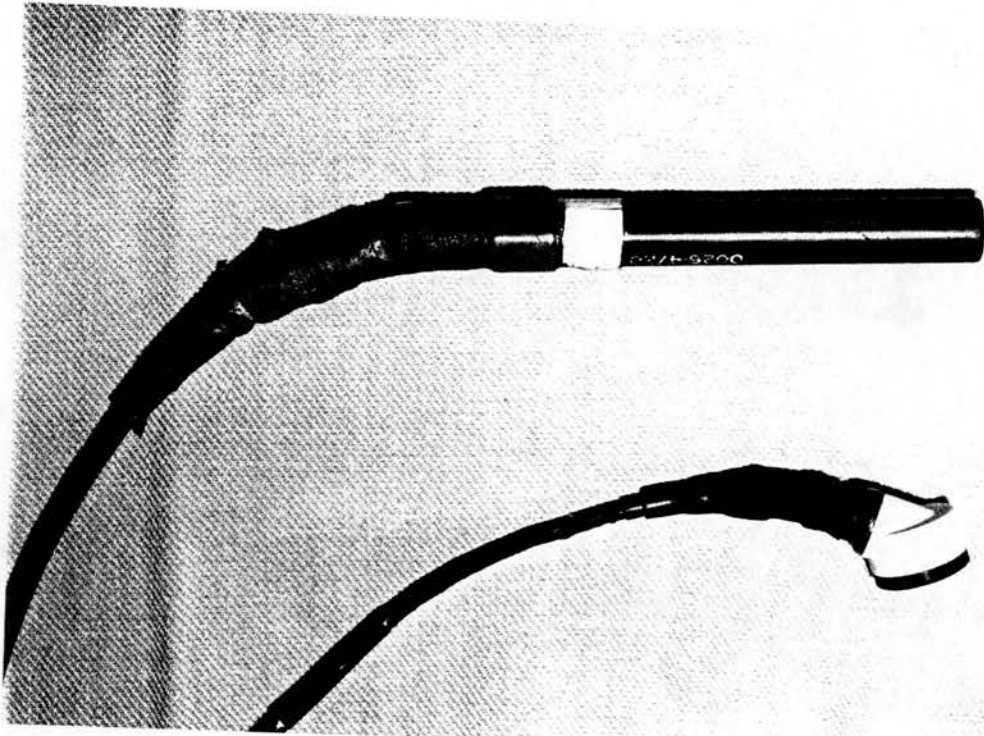
Once a signal is detected, the position from which the highest quality audible signals with the highest Doppler frequencies is obtained is the optimum position with a minimum angle of insonation. Adjustments are then made with the range-gating control, usually in incremental distances of 5mm, firstly for identification by tracking the MCA to its point of origin from the ICA. At this point the Doppler signal is bidirectional (ie. simultaneous positive and negative spectra) as the ICA divides into the MCA (seen as flow towards the probe) and the anterior cerebral artery (seen as flow away from the probe). This point serves as a useful intracranial landmark and vessel identification is aided by reference to this point. From that position the MCA can usually be tracked upwards laterally. Once the MCA is confidently identified, incremental adjustment of the depth and fine angulation movements are again made to select the maximum and best quality signals for recording. For each patient the optimal depth of recording is noted and subsequent examinations were carried out at similar positions and depths.

Additional time spent in fine adjustment of the probe is rewarding in terms of signal strength and clarity of recordings to ensure as reliable measurements as possible. This 'window optimising manoeuvre' was required whenever the probe position was lost eg due to movement or removal of probe for intermittent recordings. However with experience this procedure is fairly quick particularly when it is being repeated on the same patient. Identification of vessels by checking response to common carotid artery compression manoeuvres was not used as it was felt that this procedure would not be well tolerated in young infants and children where frequently even the duration of quiet cooperative periods for data collection was limited. To record steady reliable data, it was often necessary to use optimal settings and access the optimal position fairly quickly in young children. Maximum signal gain was thus often used especially in the initial search although on play-back for analysis this could be appropriately reduced to obtain a clear spectral outline. Operator experience with the TCD examination is essential for the reliability of data collection. All Doppler data reported in this thesis were recorded by me.

Figure 3.1: Dopek Decoder Doppler unit, audio-cassette deck with remote control box mounted on a trolley



Figure 3.2: The 2 MHz (flat, circular) and the 4 MHz (long, cylindrical) transcranial Doppler ultrasound probes

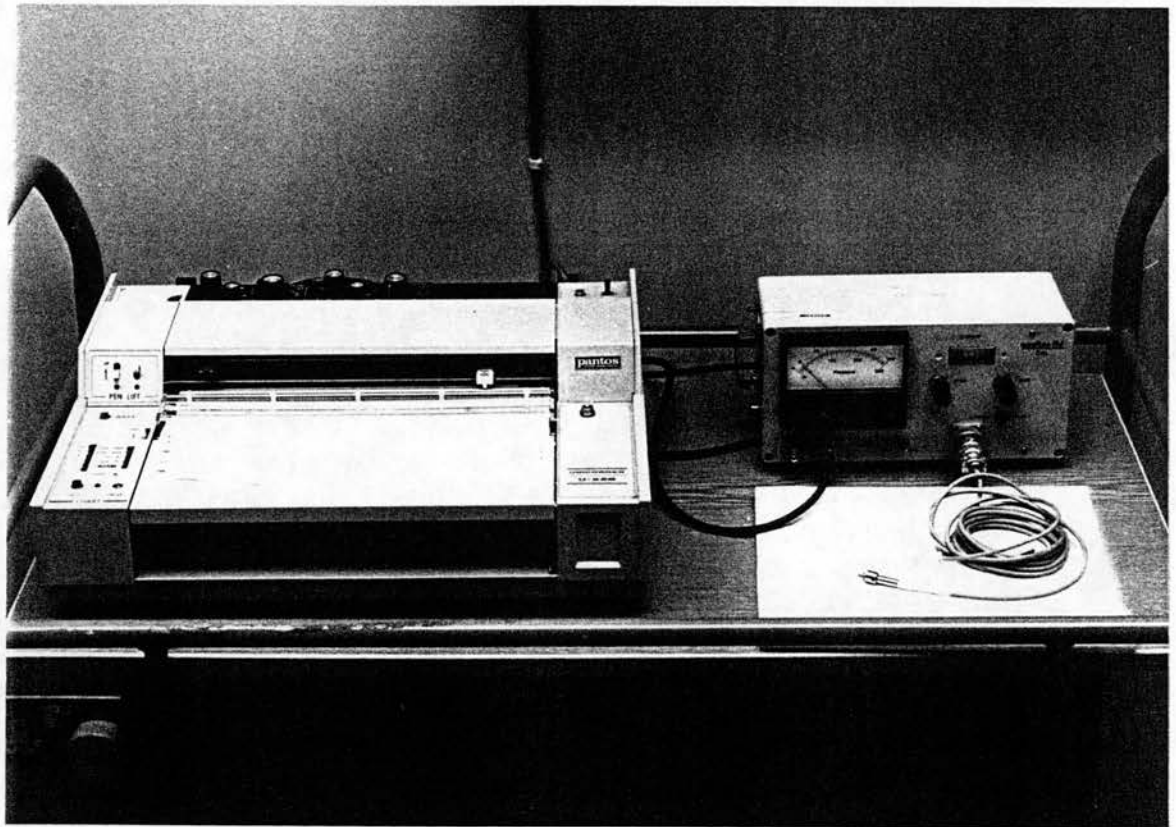


3.2 Intracranial pressure measurement

Intracranial pressure levels were always recorded from direct measurement, most commonly through a frontal reservoir, ventricular or lumbar puncture. It has been the established clinical practice in the Department of Paediatric Neurology, RHSC Edinburgh for the insertion of a separate frontal reservoir for cerebrospinal fluid (CSF) access in patients with ventricular dilatation who are thought to require repeated CSF taps or ICP measurements for assessment (Leggate et al 1989). Most patients who had ventriculo-peritoneal shunts usually also had a separate reservoir inserted. Thus in practice in those patients where reservoirs were available, ICP levels were measured through their reservoirs. Prolonged ICP recordings i.e. the sleep recordings were all performed via CSF reservoirs. In only a very few neonatal patients who were clinically judged to have significantly raised ICP necessitating reasonably urgent ventricular taps as treatment to reduce intracranial hypertension were ICP levels measured through direct transfontanelle ventricular puncture. A reservoir was usually then surgically inserted electively at a later stage if repeated taps were required to avoid the additional insult of repeated brain parenchymal puncture and formation of multiple tracks with porencephalic cysts. It was not thought ethical to perform direct ventricular puncture solely for the purpose of ICP measurement. In the meningitis study, CSF pressure recordings were obtained through lumbar puncture except for two patients who had subdural catheters in-situ.

ICP levels were measured using a nondisplacement Gaeltec (Gaeltec Ltd, Isle of Skye, Dunvegan) pressure transducer connected to a transducer control unit. This unit gives a full response to pressure changes up to 250Hz in frequency in its normal mode and the output is displayed on a meter. The transducer control unit is also connected to a 2 channel pen recorder (Gould chart recorder) where the ICP level can be continuously charted on paper. Figure 3.3 shows the Gaeltec pressure transducer, the transducer control unit and the Gould chart recorder.

Figure 3.3: The Gaeltec pressure transducer, the transducer control unit and Gould chart recorder



3.2.1 Calibration and operating procedure

The pressure transducer control unit is set up first; the 'mean/variable' switch should remain at 'variable' for calibration and recording. The pressure transducer is connected to an aneroid sphygmomanometer through a three way tap which has been primed with saline or water. The zero level is first set by adjusting the zero control knob. The control unit is then calibrated by applying pressure on the aneroid sphygmomanometer to set levels eg 50 mmHg and adjusting the gain control knob to obtain the same reading on the meter. This procedure should be repeated a number of times to check on the reliability of the reading.

Next the chart recorder is calibrated to the transducer control unit; the zero point on the chart is selected with the 'pen offset' control, the input switch is put 'on', checking that the zero level on the pen recorder and the transducer control unit remains the same. The chart recorder is then calibrated against the control unit using the calibration control knob against set pressure levels from the the manometer as before. A few calibration readings should also be checked on the chart recorder. The Gould chart recorder has a number of running speeds and can be adjusted according to the display required. After the calibration procedure, the transducer tip is sterilised by soaking in Cidex solution (2% glutaraldehyde) for 10 minutes, then rinsed off with sterile water.

The 'mean' ICP level is obtained from the sum of the diastolic ICP + $\frac{1}{3}$ ICP pulse pressure.

3.2.2 ICP measurement through a reservoir

The patient is prepared for the procedure by first shaving off any hair over the reservoir site. Next, to maintain aseptic conditions for the tap, the skin over the reservoir is scrubbed for 4 minutes with Betadine surgical scrub. After completion of the skin preparation, the reservoir is punctured with a 23-gauge butterfly needle using aseptic techniques. A backflow of clear CSF along the tubing of the butterfly needle indicates that the reservoir puncture is successful. When the CSF flow reaches the end of the tubing the sterilised transducer tip is connected on and immediately an ICP recording will be registered on the control unit meter and the chart

recorder simultaneously. The chart recorder should then be put on to run continuously at the selected speed.

It is necessary to let the patient settle after the needle puncture as most children are usually briefly distressed by the procedure. The readings should vary greatly and rise markedly when the patient is distressed if true ICP levels are being recorded. Observation of the first few minutes of recording are necessary, checking for a pattern of physiological ICP variation due to blood pressure and respiratory cycles, to confirm a reliable recording. Highly damped recordings showing no physiological variation cannot be relied upon. There are several reasons for this: (i) the presence of a blood clot within the butterfly tubing, (ii) the needle may not be in the reservoir chamber or (iii) the tip of the reservoir may no longer be in the ventricular space. Repeat needle puncture of the reservoir may be successful if either of the first two reasons are the cause of an unsatisfactory damped recording.

For brief measurements, ICP recording should run for at least 10 minutes to obtain a more reliable estimate of the 'average' level. For prolonged continuous recordings such as during overnight sleep, the butterfly needle needs to be secured in position to the head with adhesive tapes and protected with a small plastic container to avoid the child knocking it off accidentally in his/her sleep. It is also necessary to have an attendant present by the bedside throughout the monitoring to record on the chart the on-going activities during the sleeping period such as movement of the head, general restlessness, coughing, etc so that ICP or Doppler variations due to these events can be duly noted and separated from periods of spontaneous ICP and Doppler variations.

3.2.3 ICP measurement through lumbar puncture

The preparation of the patient and lumbar puncture techniques are carried out according to the usual clinical practice; i.e. the patient is positioned lying horizontally on the side, the skin over the lower lumbar spine region is cleansed with betadine solution and the spinal needle is inserted aseptically into the L4 - L5 intervertebral space. The Gaeltec pressure transducer can be connected to the spinal needle through a three-way tap. If unexpectedly, the opening CSF pressure is significantly elevated, it can be gradually reduced by running an infusion of mannitol (with an

intravenous bolus injection of frusemide) simultaneously with very slow incremental drainage of CSF through the three-way tap while still leaving the spinal needle in-situ (Minns et al 1989). The spinal needle can be safely removed when the pressure recording shows adequate reduction of pressure to normal or safe levels. This method reduces the risk of coning as a result of lumbar puncture in patients with markedly elevated ICP as by leaving the spinal needle in situ until the ICP is reduced, it avoids the leakage of CSF through the puncture site while ICP is still elevated.

3.3 Studies requiring prolonged Doppler recordings

There were three studies which required prolonged Doppler recordings and which will now be described in greater detail.

3.3.1 CBFV changes during ventricular taps

During the ventricular taps incremental volumes of CSF were drained to examine the CSF volume- cerebral blood flow velocity response. CSF was drained gradually through a 23-gauge butterfly needle inserted in a Rickham reservoir or direct ventricular puncture. ICP was measured using a nondisplacement Gaeltec pressure transducer. Doppler recordings were obtained continuously from the ipsilateral MCA during CSF drainage. Figure 3.4 shows how simultaneous ICP and Doppler measurements were recorded in an infant during a ventricular tap through a frontal reservoir. The butterfly needle (to which the ICP transducer is connected) is in the infant's reservoir while simultaneous Doppler recordings were made with the TCD probe placed in the ipsilateral temporal position. A three-way tap connected to the butterfly needle permits either CSF drainage or ICP measurement. The CSF volume withdrawn and corresponding ICP data were dubbed with the remote control microphone onto the audio tape recording Doppler data for subsequent analysis.

3.3.2 Simultaneous CBFV and ICP recordings during sleep in hydrocephalic patients

Simultaneous ICP and Doppler recordings were performed in the sleep study. ICP was continuously recorded from a frontal Rickham reservoir using a Gaeltec pressure transducer while Doppler recordings of at least 1 minute duration were obtained at 10 - 15 minute intervals from the MCA

during stable ICP states and at shorter intervals or continuously during changing ICP states. When it was possible to do so without disturbing the children's sleep, blood pressure was intermittently measured using the oscillometric method with a Dinamap machine. The simultaneous time, ICP, blood pressure and other relevant physiological data were voiced over onto the audiotape for subsequent analysis. The recording of continuous ICP measurements has been described.

3.3.3 CBFV recordings during cardiopulmonary bypass surgery

Intermittent Doppler recordings were carried out at regular intervals of 5 - 10 minute duration and continuously during specific procedures throughout cardiopulmonary bypass surgery. Simultaneous physiological data such as blood pressure and temperature, and operative procedures such as aortic clamping and declamping or commencement of non-pulsatile bypass perfusion were dubbed onto the audiotape.

In these studies measurements from each grouping of 10 consecutive waveforms were averaged as the mean values of the Doppler measurements at specific times and were used for comparison with other simultaneously collected data, such as the ICP or the mean arterial pressure (MAP).

Figure 3.4 : Simultaneous measurement of ICP through a butterfly needle inserted in a frontal reservoir and TCD measurement of MCA flow velocity using a 2 MHz transcranial probe placed in the temporal position in a young infant.



3.4 Patient groups

There were four major groups of patients in whom TCD studies were carried out which will be listed below. Further clinical details of these patients will however be elaborated on in the relevant chapters.

3.4.1 Normal children

Normal children i.e. children with no neurological disease or symptoms were studied to establish a normal range as measured with the same TCD equipment throughout the whole study. There were a total of fifty-one children, age range 1 - 15 years. They were recruited from asymptomatic siblings, outpatients or inpatients with no neurological problems or intercurrent general illness eg those who were elective admissions for minor surgery.

3.4.2 Infants and children with hydrocephalus

This group formed the main and largest study group of patients. They were further divided into sub-groups as there were separate studies to assess the effect of CSF drainage, surgical shunting, stable shunt function, non-progressive ventricular dilatation, and physiological variation during sleep on CBFV dynamics in hydrocephalic patients.

3.4.2 (i) Nineteen patients had Doppler and ICP studies performed before and after CSF drainage (taps). Eleven patients were less than 3 months old, and eight patients were between 8 months to 14 years old.

3.4.2 (ii) Twenty-four patients had Doppler studies pre- and post ventriculoperitoneal shunting or revision of blocked shunt. Nine patients were less than 3 months old, and fifteen patients were between 8 months and 12 years old.

3.4.2 (iii) Thirty-one hydrocephalic patients with functioning shunts - these patients were either:

- clinically asymptomatic, examined during routine outpatient reviews
- symptomatic patients eg with recent seizures, or irritability where subsequent investigations eg ICP measurement through their reservoirs showed that their ICP was not elevated, or their CT scans suggested evidence of a functioning shunt.

3.4.2 (iv) Ten patients who had non-progressive ventricular dilatation and remained unshunted.

3.4.2 (v) Doppler recordings were taken continuously during incremental drainage of CSF to assess CBFV response to volume change - i.e. volume-flow velocity (VFR) studies. There were nineteen patients assessed, 11 patients < 3 months old, 8 patients > 8 months old.

3.4.2 (vi) The effect of physiological variation during sleep on CBFV and ICP in hydrocephalic children was examined in seven patients. Continuous ICP recordings through a reservoir with simultaneous Doppler recordings were performed during sleep in these patients in whom there was clinical concern of intermittently raised ICP and chronic uncompensated hydrocephalus.

3.4.3 Infants and children with pyogenic meningitis

Seventeen patients; four patients less than 3 months old, thirteen patients aged between 6 months - 6 years, were serially monitored during their admission with bacterial meningitis.

3.4.4 Children undergoing cardiopulmonary bypass surgery

3.4.4 (i) Seven patients were monitored during cardiopulmonary bypass surgery.

3.4.4 (ii) One patient who suffered a hemispheric cerebral infarction after cardiopulmonary bypass surgery was serially monitored subsequent to the clinical diagnosis of her stroke.

The collection of TCD Doppler data in these patients was carried out over a period of two and a half years. Ethical approval for the TCD examinations including those performed in the normal controls was sought and granted by the Lothian Health Board Ethics Committee. Intracranial pressure measurements were performed only where clinically indicated in the management of patients with hydrocephalus and meningitis.

Chapter 4

NORMATIVE VALUES

4.1 Introduction

It is important to establish the range of variation in the CBFV indices from normal children without neurological disease to allow reliable interpretation of CBFV data obtained in pathological conditions. Normal ranges in children have been reported (see Tables 4 (i) & 4 (ii)) but it should be kept in mind that these normal ranges have been established from relatively small numbers of children within each age group (on average 20 children) and also from using different TCD equipment. Most studies have been done using TCD equipment where data is obtained from automatically computed spectral tracing. As previously discussed, these data are subject to greater variation and error depending on the signal gain intensity. Normal ranges reported in the literature may not be exactly comparable given the use of different equipment with different methods of analysis. It was thus important that as all Doppler data in this study was obtained by manual analysis, a set of normal ranges was established from data which had been collected in normal children using specifically the same equipment throughout in all the various study groups and which had been analysed in a uniform manner.

4.2 Normal controls

There were a total of 51 normal controls recruited from:

- i) siblings or relatives of in-patients; they had no known neurological conditions and no intercurrent illnesses.
n = 28
- ii) children admitted to surgical wards who had no known neurological conditions and with no systemic intercurrent illnesses, eg for elective orchidopexy, tonsillectomy, fractures.
n = 12

- iii) normal children with no known neurological conditions who were attending a growth clinic for observation of 'normal' short stature.

n = 11

Table 4 (i): Normal ranges for Resistance Index (RI) from the literature

- 1) Bode & Wais (Arch Dis Child 1988; 3: 606 - 611): calculated ranges from 112 healthy children (aged 1 day - 18yrs).

<u>Age</u>	<u>RI</u>
0 - 90 days	0.62 - 0.80
3 - 11.9 mths	0.58 - 0.62
1 - 18 yrs	0.40 - 0.59

- 2) Chadduck & Seibert (J Child Neurol 1989; 4: S77-S86) (mean \pm 2 sd)

	<u>mean RI</u>
Premature (< 33 weeks gestation):	0.77 \pm .09
Term infants (> 34 weeks gestation):	0.71 \pm .07
27 children (18 mths - 16 yrs) :	0.50 \pm .15

- 3) Schoning et al (Stroke 1993; 24: 1305 - 1309): Transcranial colour duplex sonography (mean \pm 2 sd)

	<u>mean RI</u>
< 10 yrs:	0.58 \pm .07
> 10 yrs	0.55 \pm .06
adults:	0.55 \pm .06

Table 4 (ii): CBFV values from the MCA in normal children from the literature

Authors	n	Age (yrs)	Mean	Systolic	Diastolic
				cm / sec (sd)	
Adams et al	62	3 - 17	79 (13)	126 (17)	
		4 - 8	87 (5)		
		8 - 10	82 (8)		
		10 - 14	72 (8)		
Bode & Wais	18	3 - 6	94 (100)	147 (17)	65 (9)
"	20	6 - 10	97 (9)	143 (13)	72 (9)
"	20	10 - 18	81 (11)	129 (17)	60 (8)
Brouwers et al	13	2 - 4	96 (23)	147 (30)	59 (15)
	20	5 - 9	94 (10)	139 (13)	62 (9)
	21	10 - 14	85 (19)	128 (27)	59 (14)
	22	15 - 19	75 (12)	127 (22)	51 (9)
Schoning et al (TCCD)	52	< 10	93 (13)	143 (19)	60 (12)
"	76	> 10	83 (12)	130 (190)	58 (12)

4.3 Results

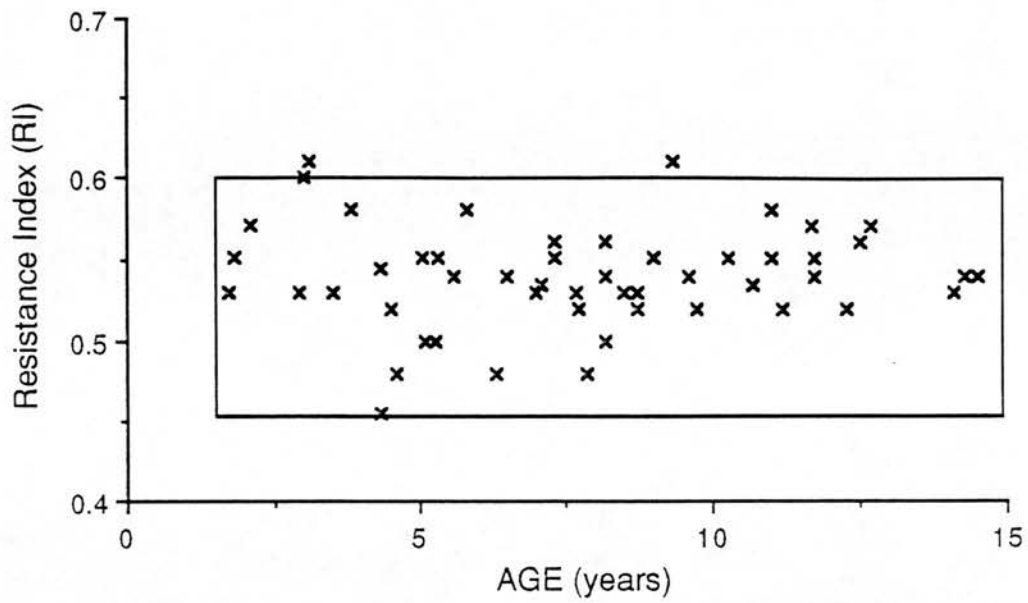
Table 4 (iii) shows mean (sd) of Doppler values from the MCA in these 51 normal children. Figure 4.1 shows the Resistance Index values from these 51 normal controls plotted against their age. Figure 4.2 shows their MFV values plotted against their age. It also shows the calculated mean (sd) values for the age groups 1 - 3 yrs, 3 - 6 yrs, 6 - 10 yrs, 10 - 15 yrs.

Table 4 (iii): Mean (sd) values of CBFV indices from the MCA in 51 normal children.

Age (yrs)	no of children	RI	MFV cm/sec	PSV cm/sec	EDV cm/sec
1 - 2.9	4	0.54 (.02)	91 (14)	154 (37)	61 (10)
3 - 5.9	14	0.54 (.05)	88 (13)	134 (20)	61 (9)
6 - 9.9	19	0.53 (.03)	88 (12)	134 (19)	62 (8)
10 - 15	14	0.55 (.02)	71 (13)	111 (18)	50 (9)

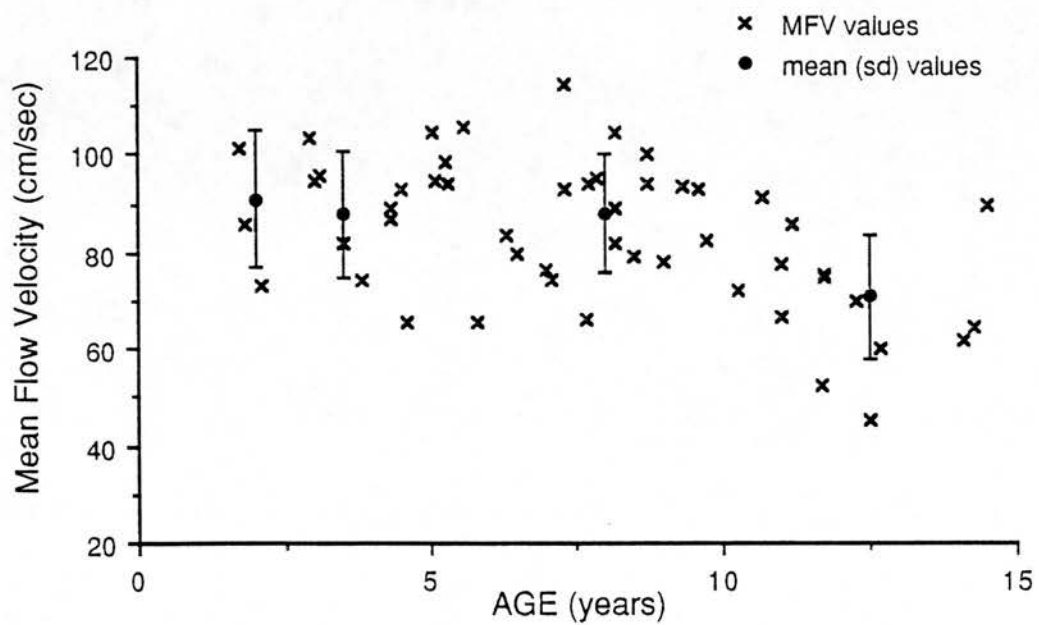
sd - standard deviation

Figure 4. 1 : RI values from 51 normal children



Boxed area represents normal range (mean \pm 2 sd)

Figure 4. 2 : Mean Flow Velocity (MFV) values from 51 normal children



Vertical bars represent mean (sd) values for age groups 1-3 yrs, 3-6 yrs, 6-10 yrs, 10-15 yrs.

4.4 Discussion

4.4.1 Effect of age on Resistance/Pulsatility indices

In this study population of normal children between the ages of 1 - 15 years there was little variation due to age on the RI value; overall the mean (\pm sd) RI was 0.54 (\pm .03), the range was from 0.46 - 0.61. Resistance Index values from normal children reported by Chadduck and Seibert (1989), and calculated from Bode and Wais's (1988) data (see Table 4(i)) are similar to the range reported above. Normal PI indices in childhood outwith infancy reported by Adams et al (1988), Brouwers et al (1990) and Bode and Wais (1988) also show a fairly stable pattern in the first two decades and indeed no trend with age is seen in normal adults as well (Adams et al 1992). Recent data using transcranial colour duplex sonography (TCCD) (Schoning et al 1993) has also shown that the RI and PI remains stable throughout childhood. This strongly suggests that RI or the PI can be reliably used for comparisons between patients in different age groups outwith infancy.

4.4.2 Effect of age on velocity values

In this study population of normal controls, there was no marked variation in the range of MFV values from the MCA between 1 - 10 years of age. There was however a fall in the MFV values in the second decade of life. PSV and EDV values show the same trend. Table 4(ii) summarising the normal ranges of MCA velocity values from the literature also show similar trends with a reduction in mean MFV values after 10 years of age. Data from Bode & Wais (1988) suggests a small increase in MFV values between the ages of 6 - 10 years. However, similar to this study normal group, Brouwers et al (1990) also did not find an increase in MFV values in the second half of the first decade and Adams et al (1988) reported decreasing MFV values in all cerebral arteries with advancing age in their patients, aged from 3 - 17 years. MCA velocity values also continue to gradually decline throughout adult life (Adams et al 1992).

Overall the reported normal ranges of Doppler velocities from the paediatric literature are remarkably similar. The velocity values obtained from this study group of normal patients were similar to the values

reported by Adams et al (1988) and generally slightly lower than the values reported by Bode & Wais (1988) and Brouwers et al (1990) although still within a similar range. This may be due in part to the manually obtained as opposed to automatically computed values reported in these other studies. More recently reported CBFV values, from transcranial colour duplex sonography in childhood and adolescence (Schoning et al 1993), which are angle-corrected measurements, are also similar to the normal ranges from TCD methods. This suggests that finding *markedly* elevated or reduced values especially compared to one's own normal ranges may be suggestive of a pathological condition, especially if there is a significant side-to-side difference. However, inter-subject comparison of absolute flow velocity values can still be unreliable as there can obviously be considerable variability of MCA calibre as well as in the angle of insonation in different patients. It is also important to bear in mind the reported intraobserver variability of 7.5 - 13% when estimating intra-subject flow variability from day to day.

Chapter 5

TCD MONITORING IN HYDROCEPHALUS

5.1 Introduction

Hydrocephalus, defined as an abnormal accumulation of fluid within the head, occurs as a result of obstruction to the normal circulation of cerebrospinal fluid (CSF) in the intracranial cavity or an imbalance between the production and absorption of CSF. It is a pathophysiological process with diverse aetiology. Raised intraventricular pressure is associated with progressive ventricular dilatation i.e. 'active' hydrocephalus (Kaiser & Whitelaw 1985). In accordance with LaPlace's theorem the initial pressure would be high to initiate ventricular dilatation and then would become relatively lower as the 'radius' of the ventricles increase. A number of physiological buffering mechanisms then come into play, such as the collapse of cerebral veins, a shunting of CSF from the ventricular to the spinal compartment and an increase in the rate of CSF absorption as a result of raised ICP. Further progression of hydrocephalus will occur when these compensatory mechanisms have been exhausted. The final stage is a state of return to normal ICP levels associated with severely dilated ventricles, i.e. 'arrested' or 'compensated', hydrocephalus. However, before this occurs significant and irreversible cerebral injury may occur as cerebral perfusion may have been compromised.

Raised intracranial pressure in the progressive stage can result either in brain ischaemia or brain shift. Secondary ischaemic damage may occur as a result of the significantly reduced cerebral perfusion pressure and also from the progressive micro- and macrovascular changes resulting from ventricular enlargement (Wozniak et al 1975). There may also be greater vulnerability in the acute stage as suggested by Hochwald et al (1975) who found that blood flow in the cerebrum, cerebellum and brain stem of cats with acute hydrocephalus was reduced by a greater proportion compared to those with chronic hydrocephalus. Using the I^{131} iodoantipyrine indicator fractionation technique Ransohoff et al (1975) also demonstrated a greater reduction in cerebral blood flow in acute hydrocephalus (22%)

than in chronic hydrocephalus (7%). Increased ICP resulted in a significant reduction in mean cerebral blood flow to the periventricular white matter and impaired molecular clearance in the caudate nucleus; this may occur even at moderately elevated ICP levels above 15mmHg (Rosenberg et al 1983). Periventricular oedema, seen as hypodense areas on the CT scan is indicative of decreased cerebral blood flow. The ependymal lining is usually thinned or disrupted and the choroid plexus may be atrophic with flattened epithelium.

In experimental hydrocephalus the vascular changes could be reversed after effective ventricular drainage and decompression (Wozniak et al 1975). Recent experimental work (Oka et al 1991) has also demonstrated that the microvascular distortion, periventricular white matter, perivascular and endothelial changes disappeared after shunting along with improvement in the regional cerebral blood flow (rCBF) in both grey and white matter. From their animal and human studies Salmon and Timperman (1977) demonstrated increased cerebral blood flow in dogs following the reduction of ICP from 10cms water to 4cms of water while in their seven patients with normal pressure hydrocephalus there were similar increases in CBF along with a reduction in cerebrovascular resistance after shunting.

Studies of CBF in adult patients with normal pressure hydrocephalus have demonstrated an improvement following shunting (Meyer et al 1985, Tamaki et al 1984) which correlated with clinical improvement. In thirty hydrocephalic infants Sato et al (1991) reported a variable distribution of rCBF reduction, detected by 123-iodoamphetamine SPECT, depending on the underlying aetiology. Neonates with congenital hydrocephalus showed either frontally dominant CBF reduction or diffuse reduction while occipitally low CBF was associated with spinal dysraphism. Most of their patients showed an increased uptake in the delayed scanning, which suggested a state of reversible ischaemia. However, in follow-up studies at a mean of 6 months after shunting there was sustained low CBF in various locations in 20% of the cases, predominantly those of dysgenetic aetiology. With PET techniques Shirane et al (1991) have demonstrated hypoperfusion and lower cerebral metabolic rate of oxygen (rCMRO₂) in the prefrontal, parietal and visual



association cortices of seven hydrocephalic children without severe neurological deficit. These recent studies indicate that disturbances in the microcirculation and tissue metabolism play a key role in the pathophysiological mechanisms of neurological deficit in childhood hydrocephalus.

The introduction of a one-way valve for internal ventricular shunting by Nulsen and Spitz (1951) ushered in the modern era of treatment of hydrocephalus. Over the years there has been a constant progression of technologic improvement in the tubing and types of shunt devices used. Cerebrospinal fluid drainage via the ventriculo-peritoneal route has now become the preferred method as ventriculo-atrial shunting has been associated with an increased rate of complications such as nephritis, endocarditis and septicaemia (Keucher & Mealey 1979). However, despite the technologic and operative improvements the complications and problems associated with shunting such as infection, obstruction, mechanical breakdown, imbalanced drainage, over-drainage and failure of the shunt to match the growth of the child still cause considerable morbidity in patients with hydrocephalus. The effects of overshunting resulting in cranio-cerebral disproportion or slit-ventricle syndrome (Epstein et al 1988) may also not be apparent for a considerable period afterwards. It is thus very important to establish the need for a shunt before embarking on this procedure.

In some patients the pathophysiologic process of ventricular enlargement may cease early, achieving a state of balance with normal levels of ICP and no further perfusion compromise i.e. 'arrested' or 'compensated' hydrocephalus before significant or irreversible cerebral insult occurs. In these patients shunting would then not be indicated. However, reliable criteria for the selection of patients who will derive clinical benefit from shunting procedures is still unclear. Patients with compensated hydrocephalus who are shunt-dependant remain at risk with complications of shunt malfunction or blockage and continue to require reliable assessment.

5.2 Assessment of hydrocephalus

In infants and children the symptoms of progressive hydrocephalus can be non-specific or even absent in a significant percentage (Kirkpatrick et al 1989). Thus reliable evaluation depends on a combination of (a) imaging to assess ventricular dilatation, (b) measurement of ventricular pressure, either directly or through reliable non-invasive transfontanometric means, and (c) assessment of cerebral perfusion changes. Diagnosis and indications for operative treatment, particularly in 'chronic' hydrocephalus, are more difficult and require careful assessment (Gaab and Koos 1984). Unpredictable results have been obtained when the decision to shunt has been based totally on ventricular size as ventriculomegaly may also be due to brain atrophy. There is no direct correlation between the level of ICP and the ventricular size (Minns 1979). The amplitude of the ICP trace, more than the mean ICP level itself has been considered by some to be a more reliable method of indicating active hydrocephalus (Foltz and Aine 1981). Prolonged ICP recordings demonstrating elevated baseline levels, with or without intermittent pressure waves, or normal baseline levels with significant intermittent pressure waves (DiRocco et al 1975, Minns 1979, Whittle et al 1985, Mori et al 1986) are likely to provide more reliable indications for shunting than isolated brief ICP measurement, although the cerebrohaemodynamic consequences of the intermittent pressure waves are still ill-defined. Various methods of investigating the CSF absorption, outflow resistance and intracranial compliance have also been undertaken by several investigators in attempting to define precise indications for shunting. CSF absorption and outflow resistance can be studied by the lumbar subarachnoid constant infusion test (Katzman and Hussey 1970) or bolus manipulation of CSF (Shapiro et al 1980) and results may be used to form indications for surgery (DiRocco et al 1977). Determination of intracranial compliance as described by Marmarou et al (1975) and Miller (1975) have been used to assess volume-buffering capacity.

The relationship between ICP and a steady increase in the volume of any intracranial content (eg brain tissue, tumour, CSF) is an exponential one, according to the modified Munro-Kellie doctrine. Thus, initially an increase in the CSF volume will cause little rise in ICP but with

progressive increase in the CSF volume, the ICP will rise steeply in an exponential fashion. The actual increase in ICP that results from a given increment in volume will depend on the ICP-volume status at that point. Miller (1975) and Marmarou et al (1975) have both described the assessment of craniospinal compliance by the manipulation of small volumes of fluid into the CSF space. Miller defines the volume-pressure response (VPR) as the increase in ICP in mmHg per ml of CSF volume added or withdrawn in one second. Marmarou and colleagues have defined the pressure-volume index (PVI) as the notional volume, which if added to the CSF, would produce a tenfold rise in ICP. This is derived from a developed logarithmic equation. These assessments, however, do not directly examine the effects of CSF volume addition on cerebral perfusion and do not account for variable adjustment within the cerebrovascular compartment. The effect on cerebral perfusion is then inferred from the expected changes in CPP. However, a means to predict cerebral haemodynamic response directly depending on the state of craniospinal compliance could help us to clarify if a given level of ICP increase in any individual patient specifically caused a deleterious effect on the cerebral perfusion.

Optimal management of hydrocephalus seeks to prevent secondary ischaemic compromise in patients with or without shunts. To do so it is necessary to have a readily available and repeatable means of assessing cerebrohaemodynamic change along with imaging facilities to assess ventricular size. In young infants serial ultrasound imaging through the anterior fontanelle is very helpful for monitoring changes in ventricular size along with the evolving intracerebral changes particularly after an intracranial haemorrhage. Duplex ultrasound will allow simultaneous Doppler measurements of flow velocity in cerebral arteries along with imaging facilities. When the anterior fontanelle has fused, CT or MRI scans are required for imaging purposes. These techniques are non-invasive but sedation or a general anaesthetic is usually required for young children which limits their repeatability. In addition, due to the radiation exposure, CT scans cannot be frequently repeated. Most techniques available for measurement of cerebral perfusion in children, as previously described, are not readily applicable for repeated bedside

assessment Transcranial Doppler ultrasound, however, is applicable to all age groups and is ideally suited for repeated assessments.

Sleep has long been recognised to be a useful physiological challenge to distinguish intermittent active from compensated hydrocephalus as intracranial pressure elevations have been noted to occur particularly during rapid eye movement and also in Stage II non-rapid eye movement sleep (Cooper & Hulme 1966, DiRocco et al 1975, Minns 1979). They occur in patients with normal awake resting ICP levels (Di Rocco et al 1975) as well as in those with a clinical diagnosis of arrested hydrocephalus (Whittle et al 1985). The clinical importance of these episodic elevations of ICP during sleep is not entirely clear although prolonged ICP measurements are evaluated in making decisions on shunting procedures in patients with chronic or clinically 'compensated' hydrocephalus (Mori et al 1986). A major concern is the secondary ischaemic insult due to significant impairment of cerebral perfusion which may occur during sustained elevation in ICP. Evaluation of simultaneous cerebral haemodynamic changes whilst monitoring ICP in these children could help to determine the clinical importance of these events during sleep.

5.3 Doppler studies in hydrocephalus

Hill and Volpe (1981) first applied the use of Doppler ultrasound to study cerebral blood flow velocity in eleven patients with infantile hydrocephalus. They reported increased RI of anterior cerebral artery waveforms which they associated with the severity of ventricular dilatation. Since then other Doppler studies, either from duplex scans through the anterior fontanelle in young infants or TCD scans in older infants and children, have reported varying effects on waveform pulsatility and variable contributions of PSV or EDV to pulsatility changes. Few studies have reported on ICP levels in their patients, either from direct or transfontanelle measurements. Most have made assumptions about the likely presence or absence of raised ICP from the clinical state.

The RI and the PI have both been commonly applied in hydrocephalic patients. Both indices, being ratios, thus minimise the error in estimating true velocity due to a varying angle of insonation. This may be more

important in hydrocephalus as the vascular anatomy could be significantly distorted by ventricular enlargement and a small angle of insonation cannot be safely assumed (Finn et al 1990).

5.3.1 Studies reporting no diagnostic value of pulsatility indices

Most studies have found increased pulsatility in patients with progressive or 'symptomatic' hydrocephalus. Only two studies (Grant et al 1987, Anderson & Mawk 1991) have concluded that pulsatility indices did not contribute significant diagnostic information in hydrocephalus. Grant et al did not find significantly raised RI in their hydrocephalic patients but only 3 of their 10 patients had overt clinical signs of raised ICP. Anderson and Mawk reported increased pulsatility in only 31% of their hydrocephalic patients requiring shunting when mean pulsatility was also generally increased in all their patient groups except those with ventriculomegaly without haemorrhage or shunts. However, as ICP was not measured in either study it is not clear if some of these patients may have been in a stable state without raised ICP.

5.3.2 Studies relating ICP to waveform pulsatility

5.3.2 (i) Experimental evidence

Seibert et al (1989) measured ICP directly in 4 dogs from a frontal lobe fibreoptic monitor (Camino) with simultaneous Doppler recordings. They found a direct correlation between ICP, cerebral perfusion pressure and RI.

5.3.2 (ii) Transfontanelle pressure measurements

Hill and Volpe (1981) reported elevated transfontanelle pressure with elevated RI in all but 2 of their patients. However, they concluded that ventriculomegaly was a more critical factor than raised ICP in the pathogenesis of impaired flow as these 2 patients also had an elevated RI and 4 patients with the most marked ventriculomegaly had the most markedly elevated RI. However, more recent studies (Hanlo 1990, Horikawa 1991) have reported a direct relationship between increased pulsatility and raised transfontanelle pressure.

5.3.2 (iii) Direct ICP measurements

Data from 13 patients reported by Chadduck et al (1991) suggests a reliable linear relationship between RI and ICP beyond the normal range for RI (between 0.45 - 0.6) obtained by TCD study. Pople et al (1991) have also found a significant correlation between the PI and intraventricular pressure in 14 patients whose pressure levels were estimated by tapping their shunt system. However, in three neonatal infants Quinn et al (1992) reported no correlation between RI and ICP.

5.3.3 Relationship between ventricular dilatation and waveform pulsatility

A number of studies have shown that stable ventriculomegaly is associated with normal pulsatility (Deeg et al 1988, Norelle et al 1989, Anderson & Mawk 1991, Huang & Chio 1991). In common with Hill and Volpe's findings, a corresponding trend between increased RI with increasing ventricular dilatation was reported by Lui et al (1990). However, absent diastolic flow also occurred in 2 infants with only moderate ventricular dilatation and raised ICP was suspected to be a contributory factor although ICP was not measured at all in this study. Horikawa (1991) reported that after shunting there was a rapid fall in waveform pulsatility while ventricular size was only slightly reduced thus suggesting that changes in pulsatility were mainly affected by ICP.

5.3.4 CBFV changes pre- and post- drainage (taps and shunts)

All studies of doppler CBFV changes pre- and post CSF drainage by CSF taps or shunting (Hill & Volpe 1981, Deeg et al 1988, Seibert et al 1989, Van Bel et al 1988, Norelle et al 1989, Nishimaki et al 1991, Horikawa 1991) have consistently shown that pulsatility is significantly decreased after effective CSF drainage. In a study of eight neonatal patients, Quinn et al (1992) found that RI was significantly reduced after tapping in those with raised ICP but not in three taps when opening ICP was not raised.

5.3.5 Effect of PSV and EDV on pulsatility indices

Two studies which further analysed components of the RI reported that the increased RI in hydrocephalus was due to increased PSV (Alvisi et al 1985, Van Bel et al 1988) which the authors attributed to increased cerebrovascular compliance. ICP was not measured in either of these two

studies. However, other recent studies have shown that the increased pulsatility is due to marked decrease in EDV (Deeg et al 1988, Huang & Chio 1991). Deeg et al (1988) found a significant increase in the pulsatility index associated with a significant decrease in the end-diastolic velocity in 26 children with marked and rapidly progressive hydrocephalus. After shunting a significant fall in pulsatility and increase in EDV were reported.

5.3.6 Use of Doppler indices in clinical management

5.3.6 (i) Monitoring shunt malfunction

Shunt malfunction is associated with raised ICP as most ventricular shunts are either totally or mostly pressure regulated. Raised pulsatility (both RI and PI) has been reported to be a reliable indicator of shunt malfunction (Chadduck et al 1991, Pople et al 1991). In 41 patients with shunt malfunction RI decreased from 0.71 ± 0.1 to 0.53 ± 0.12 following revision while 11 patients with functioning shunts had RIs of 0.47 ± 0.05 (Chadduck et al 1991). Of the 63 children admitted with suspected shunt blockage (Pople et al 1991), 18 of the 32 cases with surgically confirmed blocked shunts had a PI value greater than 2 sd above the mean for their age for asymptomatic shunted children. Only one of the 31 cases not requiring surgical intervention had a value outside the normal range.

5.3.6 (ii) Assessment of patients requiring shunting

A few studies suggest that waveform pulsatility, either the RI or PI, can be useful in selecting those with progressive hydrocephalus who require shunting. Chadduck et al reported a mean RI of 0.84 in 46 neonates with symptomatic or progressive ventriculomegaly requiring shunts which decreased to 0.72 after shunting. Both Horikawa (1991) and Nishimaki et al (1992) have also found similar RI values; suggesting RI values >0.8 as criteria for shunting or judging shunt effectiveness in young infants. In 24 patients, aged 7 days to 14 years, Norelle et al (1989) found raised mean values of 1.72 in those with symptoms prior to shunt placement which decreased to 1.02 after shunt placement while those with stable ventriculomegaly had a lower mean PI value of 1.06. Huang and Chio (1991) reported that only patients who had an elevated RI before shunting derived benefit while a group of infants with atrophic ventriculomegaly

who did not have a significantly raised RI before shunting did not benefit from the procedure. Surprisingly at operation ICP measured from the lateral ventricles before shunting was not significantly different between the two groups in their study.

5.3.7 Doppler studies in fetal hydrocephalus

Doppler ultrasound has also been applied to study intracranial velocity waveforms in fetal hydrocephalus. Degani et al (1988) found progressive elevation of the pulsatility index proportional to the developing ventriculomegaly in 4 fetuses and suggested that this could be useful for the determination of optimal timing of intervention. In contrast Kirkinen et al (1988) found that there was no obvious correlation between ventricular dilatation and the intracranial velocity waveforms in the 9 hydrocephalic fetuses which they studied. The reliability of intracranial Doppler waveforms in fetuses is even more difficult to determine as there are considerable technical restrictions.

Thus at the present time while there has been a number of experimental and clinical studies of intracranial arterial Doppler flow velocity patterns in hydrocephalus there remains considerable debate with regard to the interpretation of the Doppler changes seen. This is in part due to the lack of correlation with reliable ICP measurements in clinical conditions. There have been few attempts to study dynamic cerebral blood flow velocity changes in response to intracranial volume changes. There is also the striking absence of any reports of more prolonged or continuous Doppler recordings in hydrocephalic patients to examine CBFV variability in different physiological conditions such as sleep. As periods of abnormal ICP elevations with plateau (A), B or C intracranial pressure waves may not be revealed from brief recordings in the awake state, it thus follows that brief or isolated measurements of CBFV may also fail to reveal periods of significant cerebrohaemodynamic changes in these patients. Interpretation of brief, isolated Doppler findings without corresponding measurement of ICP may thus be unreliable or inconclusive.

The objectives in the TCD studies on hydrocephalic patients will be to seek further clarification of the Doppler values obtained during various clinical

conditions in childhood hydrocephalus to enable better informed interpretation. In particular the usefulness of more prolonged Doppler studies with simultaneous ICP recordings as well as the examination of dynamic CBFV changes with CSF volume manipulation will also be assessed. The TCD studies are subdivided into six groups to examine Doppler characteristics before and after ventricular taps, before and after ventriculo-peritoneal shunting, in patients with stable shunt function, in patients with stable ventricular dilatation, during CSF drainage, and variation during sleep. By assessing Doppler characteristics in hydrocephalic patients in a range of manipulated or physiological conditions we may be able to interpret more reliably the Doppler values obtained for useful clinical application.

5.4 Patients

There were six separate study subgroups to assess the effect on CBFV dynamics of

- (i) CSF drainage by ventricular taps,
- (ii) CSF drainage by surgical shunting,
- (iii) stable shunt function,
- (iv) stable ventriculomegaly
- (v) CSF volume drained - CBFV response,
- (vi) physiological variation during sleep.

5.4.1 The effect on CBFV of directly draining CSF through ventricular taps was examined by performing simultaneous TCD examinations with direct ICP measurements just before and after CSF drainage. A total of 61 taps with simultaneous pre- and post-tap Doppler studies were carried out in 19 patients with hydrocephalus: 52 taps were carried out on 11 young infants, aged from birth to 3 months of age - (Group I), and 9 taps were carried out in 8 older infants and children aged between 8 months to 14 years 3 months (Group II). Four of the group II patients were between 8 to 17 months, while four were between 4 yrs to 14 years 3 months. The underlying aetiology of their hydrocephalus is listed in Table 5 (i). Paired t-test analysis was carried out for CBFV and ICP values before and after CSF drainage. A correlation coefficient was calculated for corresponding

CBFV and ICP values in both groups of patients and in individual patients where there were sufficient data from repeated taps.

5.4.2 TCD examinations were performed in quiet bedside conditions in 23 patients with hydrocephalus before and after ventriculo-peritoneal shunt (VPS) insertions or revisions. Nine of these patients were under 3 months of age (Group I: median age 3 weeks), and 14 were between 4.5 months to 12 years 8 mths (Group II: median age - 13 months). The clinical details of these patients are listed further on in Table 5 (v). Most patients had a number of TCD examinations carried out serially on a number of days both before and after their shunt procedure and the mean Doppler values pre-operatively for each individual patient were compared to mean values post-operatively by paired t-test.

5.4.3 Thirty-one hydrocephalic patients with stable functioning shunts were studied. Their age range was from 3 months to 13 years 1 month (median age 35 months), ten patients were less than 12 months of age. These patients were either:

- clinically asymptomatic, examined during routine outpatient reviews or
- symptomatic patients eg. with recent seizures, or irritability where subsequent investigations such as ICP measurement through a reservoir tap showed that ICP was not elevated or CT scans which showed well-controlled hydrocephalus with no evidence of raised ICP.

Doppler data from 21 of these patients who were >12 months of age were statistically compared with Doppler data from the normal control group.

5.4.4 TCD examinations were performed on ten patients who had non-progressive ventricular dilatation and remained unshunted. The Doppler values from this group were compared against the values from the normal controls.

5.4.5 Doppler recordings were taken continuously during incremental drainage of CSF to assess CBFV response to volume change - i.e. volume-flow velocity (VFR) studies. There were nineteen patients assessed, 11 patients <3 months old, 8 patients between 8 months to 14 years 3 months

old. Serial RI values throughout the tap were plotted against CSF volume drained for each tap to examine the pattern of rate of change in RI.

5.4.6 The effect of physiological variation during sleep on CBFV and ICP in hydrocephalic children was examined in seven patients in whom there was clinical concern of intermittently raised ICP and chronic uncompensated hydrocephalus. Continuous ICP and simultaneous Doppler recordings at frequent intervals were obtained during sleep in eight studies; one child was studied before and after a skull morcellation procedure.

5.5 Results

5.5.1 Pre- and post-ventricular CSF taps study

The underlying aetiology of hydrocephalus in the 19 patients is shown in Table 5 (i). All but 3 of the taps carried out in the young infants (Group I) were prior to any shunt procedure and were performed for assessment and therapeutic reasons when there was clinical suspicion of raised ICP or evidence of progressive ventricular dilatation from serial ultrasound scans. One infant had 3 further CSF taps for therapeutic reasons to reduce ICP after her first ventriculo-peritoneal shunt was blocked by cellular debris. Five of the Group II patients had existing ventriculo-peritoneal shunts (VPS) and the taps were performed when they presented with clinical symptoms of raised ICP or cerebral imaging evidence of increased ventricular dilatation suggesting blocked or poorly functioning shunts.

Table 5 (i) Aetiology of hydrocephalus in patients in ventricular CSF taps study.

	<u>Aetiology</u>	<u>No. of patients</u>
Group I :		
	myelomeningocele	6
	post-haemorrhagic	1
	congenital X-linked	1
	aqueduct stenosis	1
	perinatal haemorrhage/ infection	2
Group II:		
	post-haemorrhagic	4
	myelomeningocele	1
	aqueduct stenosis	1
	post-meningitis	1
	post-traumatic	1

Table 5 (ii) Mean ICP and CBFV values pre- and post- ventricular CSF taps in Group I patients (neonates and young infants)

	no of taps	Pre-tap mean (sd)	Post-tap mean (sd)	t-statistic	p value
RI	52	0.78 (.05)	0.68 (.06)	18.26	<0.001
MFV (cm/sec)	52	40.4 (11.8)	48.7 (13.0)	-8.23	<0.001
PSV (cm/sec)	43	75.7 (18.1)	79.7 (19.4)	- 3.29	0.002
EDV (cm/sec)	43	16.0 (6.0)	25.1 (8.1)	-12.87	<0.001
ICP (mmHg)	50	11.2 (3.2)	4.9 (1.8)	17.95	<0.001

Table 5 (iii) Mean ICP and CBFV values pre- and post- ventricular CSF taps in Group II patients (older infants and children)

	no of taps	Pre-tap mean (sd)	Post-tap mean (sd)	t-statistic	p value
RI	9	0.62 (.07)	0.53 (.06)	6.87	0.000
MFV (cm/sec)	9	61.0 (16.2)	73.6 (16.4)	- 3.82	0.005
PSV (cm/sec)	9	99.4 (27.4)	108.7(27.5)	-2.05	0.075 (ns)
EDV (cm/sec)	9	37.7 (11.6)	49.4 (13.4)	-4.64	0.002
ICP (mmHg)	8	14.6 (3.4)	6.9 (2.4)	4.48	0.003

ns - not significant

5.5.1 (a) ICP and CBFV changes pre- and post- ventricular taps

Tables 5 (ii) and 5 (iii) show the mean ICP and CBFV values in both groups of patients before and after ventricular CSF taps. In both groups there was a highly significant decrease in RI ($p < 0.001$) with an increase in MFV ($p < 0.001$, $p < 0.01$ in Groups I and II respectively) associated with the expected reduction in ICP. Figure 5.1 shows the change in RI in the individual Group II patients after CSF taps. As the value of the RI can be affected by changes in PSV or EDV, these indices were also assessed. There was a more significant increase in EDV ($p < 0.001$) compared to the increase in PSV ($p < 0.01$) in Group I patients. In Group II patients only the change in EDV was statistically significant ($p < 0.01$). The RI decreased consistently after CSF drainage in all 61 taps while the increase in MFV was less consistent. After 3 taps there was a small decrease in MFV and PSV although there was still a consistent increase in EDV thus RI also decreased in these 3 taps. These results indicate that the increase in EDV was the main velocity component contributing to the observed decrease in RI. There was no significant change in ventricular size in these patients

after CSF drainage, thus the increased RI pre-tap was not likely to be due to ventricular dilation per se.

5.5.1 (b) Correlation between CBFV indices and ICP

Group I:

There was no correlation between any of the CBFV indices and ICP for the data from the whole group taken together. However, in four neonatal patients who had repeated CSF taps there was a statistically significant correlation between RI and ICP values for each individual patient. Table 5 (iv) shows the correlation between RI and ICP in each of these patients. Hydrocephalus was associated with perinatal infection in patients LF and RA, and with lumbosacral myelomeningoceles in patients MR and CM. Although the correlation coefficient values range from 0.61 to 0.87, the highly significant relationship nevertheless reflects a reliable correlation between increasing RI and ICP, particularly for each individual patient.

Table 5 (iv) Correlation between individual RI and ICP data obtained during CSF taps in 4 neonatal patients

Patient	no of taps	r value	t - statistic	p value
LF	31	+ 0.61	4.14	< 0.001
RA	38	+ 0.64	4.97	< 0.001
MR	20	+ 0.78	5.29	< 0.001
CM	14	+ 0.87	6.19	< 0.001

Group II:

There was a statistically significant correlation between RI and ICP values in Group II patients for the whole group; $n = 17$, $r = 0.695$, $p < 0.01$, as shown in Figure 5.2 There was no correlation between MFV, PSV or EDV values with ICP.

Figure 5.1: RI values pre / post CSF taps in group II patients

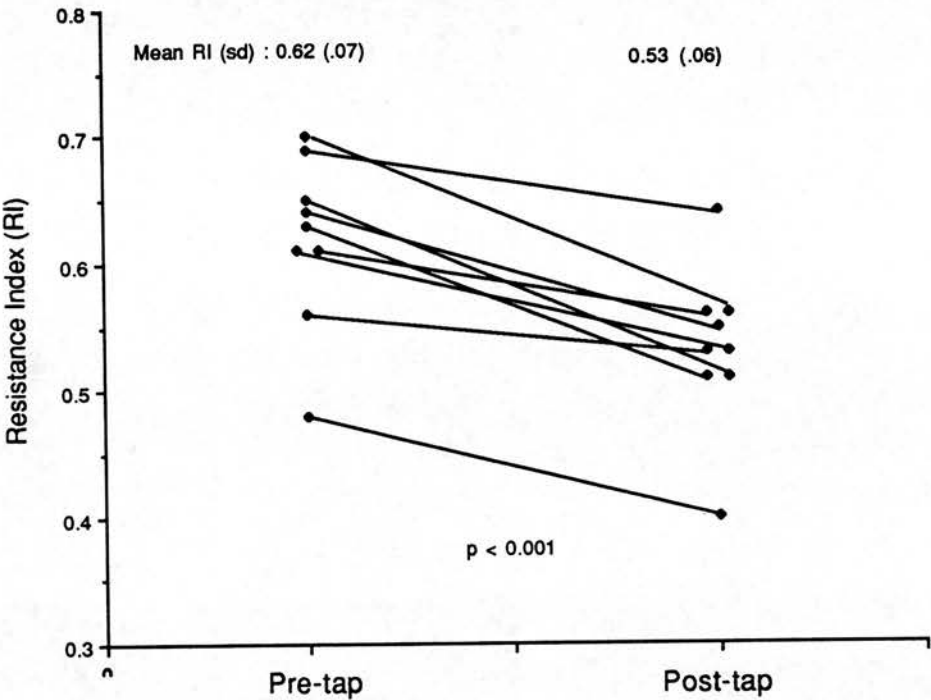
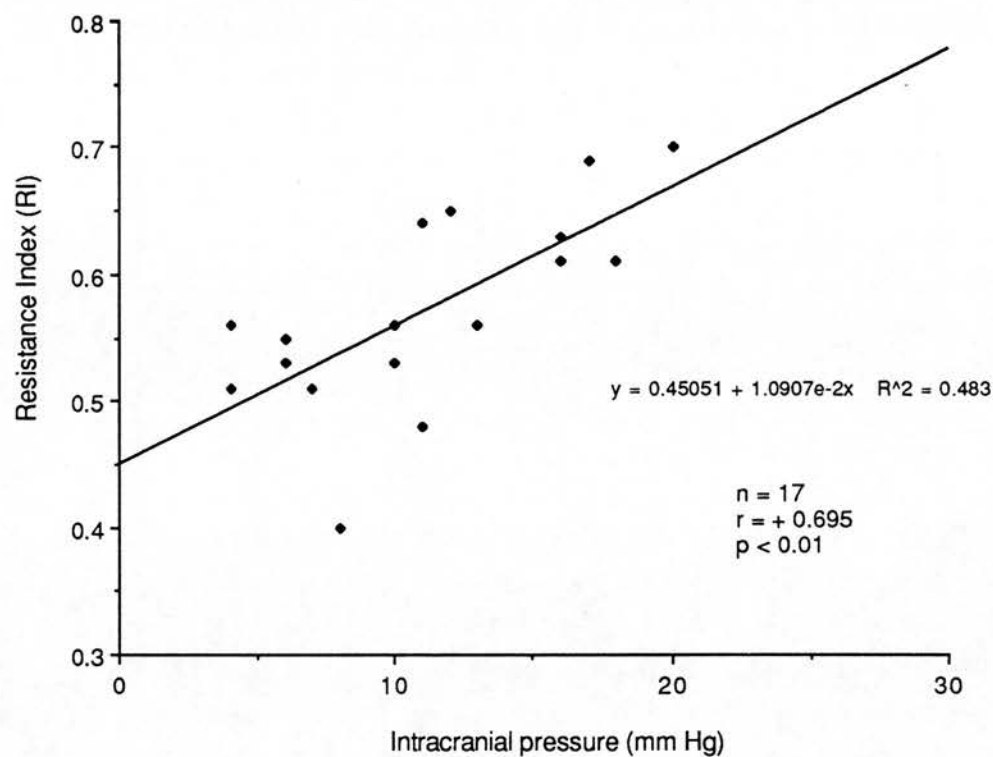


Figure 5. 2: correlation between RI and ICP in Group II patients



5.5.2 Pre- and post- ventriculo-peritoneal shunting study

The clinical details of the patients in the ventriculo-peritoneal shunting study are summarised in Table 5 (v). All the Group I and six of the Group II patients were shunted for the first time. One term infant had gross X-linked congenital hydrocephalus (head circumference at birth - 49cm), five infants with myelomeningoceles developed increased ventricular dilatation after primary closure of the myelomeningocele; one infant with perinatal infection and one with prenatal haemorrhage developed progressive ventricular dilatation and raised ICP with no evidence of 'arrest' or compensation after a period of observation with intermittent ventricular taps. Early shunting was performed in 5 infants with aqueduct stenosis who presented with significant clinical signs of intracranial hypertension eg 'sunsetting', marked irritability and vomiting with a tense anterior fontanelle or progression of ventricular dilatation. One infant who had initial drainage with marsupialisation of a suprasellar arachnoid cyst, and another infant with congenital hydrocephalus and associated congenital cyanotic heart disease were shunted when they developed clinical signs of raised ICP, and cerebral imaging showed significant ventricular dilatation. One patient aged 12 years, developed signs of raised ICP after surgical removal of a cerebellar astrocytoma which had bled on initial presentation.

Eight of the Group II patients had revision of existing VP shunts. Six of them presented with symptoms suggestive of blocked shunts i.e headaches, drowsiness, vomiting or pain at the back of the neck. One patient presented with chronic symptoms of raised ICP with increasing clumsiness, ataxia and deterioration in academic progress; her CT scan showed increased ventricular dilatation confirming poor shunt function. One patient was clinically asymptomatic but the rate of head circumference growth had increased and his CT scan showed further increase in ventricular size confirming poor shunt function.

Three Group I patients developed complications after their first VP shunt, two had ventriculitis while one had a blocked shunt due to cellular debris. In the two patients with ventriculitis, the infected shunt was removed and the CSF sterilised by a period of combination antimicrobial chemotherapy with intravenous and intra-intrathecal antibiotics which were

administered through a separate reservoir. CSF was taken each day during the ventricular taps for therapeutic drainage and also sent off for analysis of leucocyte count and differential to assess the efficacy of the antimicrobial therapy. When the CSF was fully sterilised a new VP shunt and reservoir were then reinserted. In these three patients the preoperative values were compared to the postoperative values after the second functioning shunt and the Doppler values from the in-between period with ventriculitis or blocked shunt were not included in the analysis.

Table 5 (v) Clinical details of patients undergoing VPS operation

Patient	Sex	Age	Aetiology	existing VPS (+/-)
<u>Group I (n = 9)</u>				
LF	F	1 mth	perinatal infection	-
MG	M	1 wk	congenital X-linked	-
JMcC	M	2 wk	myelomeningocele	-
TS	M	1 wk	myelomeningocele	-
RA	F	1 mth	prenatal haemorrhage	-
MR	F	2 mth	myelomeningocele	-
CM	F	2 wk	myelomeningocele	-
SG	F	2 mth	aqueduct stenosis	-
<u>Group II (n=14)</u>				
LP	F	10 mth	arachnoid cyst	-
WB	M	6 yr 1 mth	aqueduct stenosis	+
PB	M	12 mth	myelomeningocele	+
IF	M	14 mth	post-haemorrhagic	+
AM	F	12yr 8mth	cerebellar astrocytoma	-
CJ	F	4 yr	post-haemorrhagic	+
KO	M	9yr 6mth	myelomeningocele	+
CG	F	11yr 9mth	myelomeningocele	+
GB	M	4 mth	aqueduct stenosis	-
TS	M	12 mth	myelomeningocele	+
NB	F	8 mth	congenital	-
SD	M	4 mth	aqueduct stenosis	-
JC	F	8 mth	aqueduct stenosis	-
SH	F	6yr 1mth	post-haemorrhagic	+

VPS - ventrico-peritoneal shunt

5. 5. 2 (a) CBFV changes pre- and post- ventriculo-peritoneal shunting

The mean CBFV values before and after successful ventricular peritoneal shunting in the Group I and II patients are shown in Tables 5 (vi) and (vii). All patients who were symptomatic prior to shunting improved after successful shunting. In both groups RI decreased significantly postoperatively ($p < 0.001$), mean (sd) RI in Group I decreased from 0.75 (.04) to 0.68 (.06), and in Group II from 0.67 (.06) to 0.55 (.05). Figures 5.3. and 5.4 show the decrease in RI after shunting in the Group I and Group II patients respectively. There was an accompanying significant increase in MFV in both groups. The decrease in RI was due to an increase in EDV ($p < 0.001$) rather than to change in PSV. There was an increase in PSV which was only statistically significant in the Group I patients ($p < 0.01$). The pattern of change was identical to that observed with ventricular CSF taps; and the value of the indices before and after shunting were indeed very similar to the values obtained pre-and post-taps. Intracranial pressure was not checked postoperatively in those who were well with no clinical signs of shunt malfunction as reservoir puncture would have been invasive with the added risk of introducing infection.

In the Group I patients where ultrasound imaging through the anterior fontanelle was possible, ventricular dilatation before and after ventriculo-peritoneal shunting was compared. In these infants there was no significant immediate change in ventricular size after shunting although there was a highly significant change in the CBFV values within the early postoperative period. Over subsequent months in the infants whose shunts continued to function effectively there was gradual reduction in ventricular size, seen on repeated ultrasound scans.

Table 5 (vi) Mean CBFV values pre- and post ventriculo-peritoneal shunting in Group I patients (neonates and young infants)

Doppler indices	n	Pre - VPS mean (sd)	Post - VPS mean (sd)	t-statistic	p value
RI	9	0.75 (.04)	0.68 (.06)	6.857	0.000
MFV (cm/sec)	9	39.2 (13.0)	52.3 (12.8)	-9.10	0.000
PSV (cm/sec)	9	72.8 (21.8)	84.1 (19.8)	-3.6	0.007
EDV (cm/sec)	9	17.9 (6.2)	27.5 (7.7)	-8.3	0.000

n - no of patients

Table 5 (vii) Mean CBFV values pre- and post ventriculo-peritoneal shunting/revision in Group II patients (infants and children)

	n	Pre -VPS mean (sd)	Post - VPS mean (sd)	t-statistic	p value
RI	14	0.67 (.06)	0.55 (.05)	7.37	0.000
MFV (cm/sec)	14	56.0 (10.7)	71.2 (13.5)	-3.55	0.004
PSV (cm/sec)	14	99.2 (16.3)	105.1 (19.6)	-0.95	0.36 (ns)
EDV (cm/sec)	14	33.3 (8.6)	47.3 (8.9)	-4.87	0.000

ns - not significant

n - no of patients

Figure 5. 3 : RI values pre / post ventriculo-peritoneal shunting in Group I patients

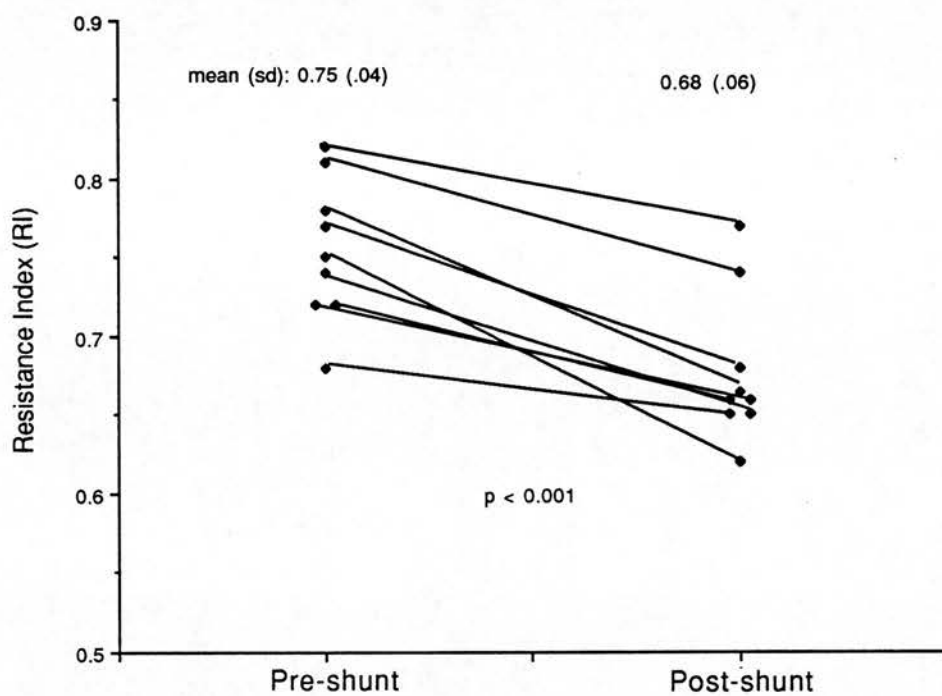
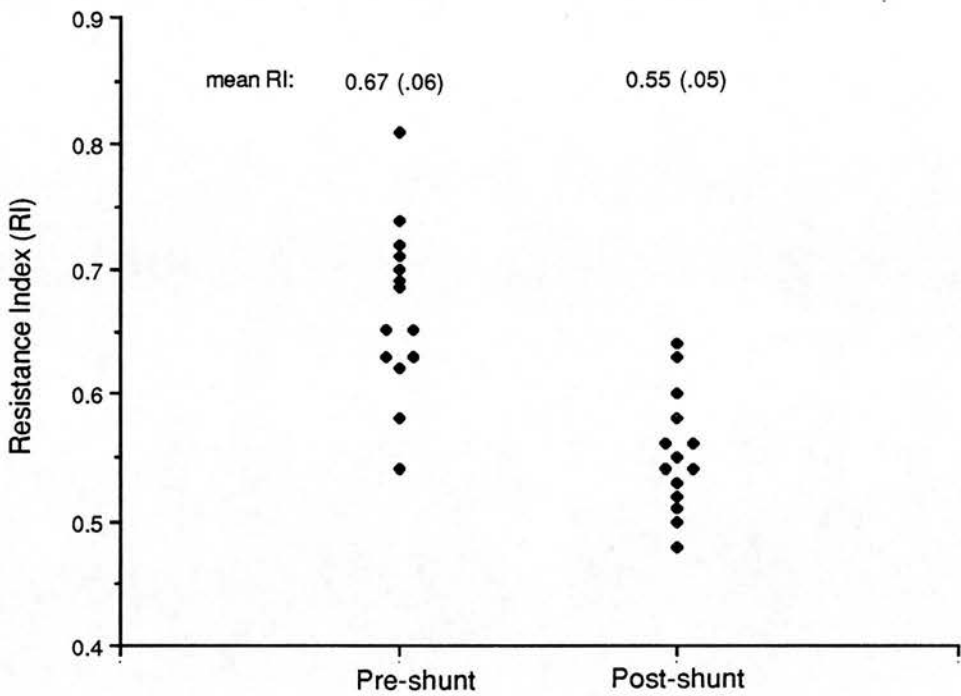


Figure 5.4 : RI values pre / post ventriculo-peritoneal shunting in Group II patients



5.5.2. (b) Case Illustrations:

Case 1: Patient MG had gross X-linked congenital hydrocephalus. Mean serial RI and MFV values over the first four days of life prior to his first VPS and frontal reservoir insertion on day 5 was 0.73 and 38 cm/sec. On the first postoperative day, RI had decreased to 0.65 and MFV was 37 cm/sec. However, he developed ventriculitis post-operatively requiring removal of his VPS and he received intravenous and intrathecal antibiotics through his reservoir for two weeks. He had a replacement VPS performed and his postoperative course after this second VPS was uncomplicated. Mean serial RI and MFV during the period with ventriculitis between the first and second shunt was 0.69 and 35 cm/sec and subsequently following the second shunt was 0.66 and 54 cm/sec. Thus the CBFV values suggested consistently improved flow only after the second successful VPS which was uncomplicated by postoperative ventriculitis. His subsequent cerebral ultrasound scans after the second VPS showed a steady decrease in ventricular size.

Case 2: Patient LF had hydrocephalus diagnosed on an antenatal scan just prior to delivery, which was thought to be possibly due to a prenatal intraventricular haemorrhage as postnatal scans showed evidence of thrombus in the posterior lateral ventricles. Ventricular dilatation progressed despite repeated ventricular taps through a frontal reservoir (ICP was between 7 and 10 mmHg) and the first VPS was performed at 5 weeks. Mean RI and MFV before the first VPS was 0.78 and 46 cm/sec. However, there was no significant clinical improvement or change in ventricular size and head circumference measurement postoperatively. Repeat ICP measurement from ventricular taps after the first VPS showed that ICP remained elevated between 8 - 9 mmHg. A second VPS was performed seven days later and the first VPS was found to be proximally blocked by cellular debris. Mean RI and MFV between the first and second VPS was 0.76 and 54 cm/sec and after the second successful VPS was 0.66 and 64 cm/sec. Serial CBFV values in this patient again illustrated improvement in flow only after the second successful VPS and gave additional indication of inadequate shunt function after the first blocked VPS.

Case 3: Patient LP was referred at the age of ten months with a head circumference over the 97th centile which had increased from the 50th centile at six months of age. Her anterior fontanelle was tense on palpation. Cerebral ultrasonography and CT scan showed dilated lateral ventricles with a suprasellar arachnoid cyst. The initial RI was 0.72. Operative drainage with marsupialisation of the cyst and insertion of a frontal reservoir was performed. Initially there was some clinical improvement and very slight decrease in ventricular size and mean RI was then 0.56. However, within twelve days she was again more irritable with a tense fontanelle and her ultrasound scan showed an increase in the size of the ventricles and the suprasellar cyst again. From a reservoir tap she was found to have raised ICP at 15 mmHg. At that time the mean RI was 0.63. A ventriculo-peritoneal shunt was then performed with subsequently marked clinical improvement and while there was no significant change in ventricular size, mean RI after ventriculo-peritoneal shunting was further decreased to 0.5. Clinical improvement after shunting was sustained and thus although the lateral ventricles remained significantly dilated, they did not appear any longer to be under raised pressure.

These cases illustrate the use of serial CBFV values, in particular the RI for non-invasively monitoring progress after shunting.

5.5.3 Functioning shunt study

Thirty one patients had TCD studies performed when their ventriculo-peritoneal shunts were known to be functioning. Their age range was from 3 months to 13 years 1 month (median age 35 months), ten patients were less than 12 months of age. The underlying aetiology of their hydrocephalus is summarised below in Table 5 (viii).

Table 5 (viii) Aetiology of hydrocephalus in patients with functioning shunts

<u>Aetiology</u>	<u>number of cases</u>
myelomeningocele	10
post-haemorrhagic	6
aqueduct stenosis	7
post-meningitic	3
severe, congenital	2
arachnoid cyst	1
perinatal infection	1
idiopathic	1
Total number:	<u>31</u>

Eighteen of these patients had TCD examinations performed at routine out-patient visits when they had no signs or symptoms of shunt malfunction. One patient was examined during an admission for a urinary tract infection and also had no signs or symptoms associated with her ventriculo-peritoneal shunt at the time.

Twelve patients had symptoms which could have been associated with acute or chronic shunt malfunction; however, in all 12 patients this was subsequently excluded with further investigation either by direct ICP measurement through their ventriculostomy reservoir, or CT scans which showed well-controlled hydrocephalus with no increase in ventricular dilatation and no evidence of raised ICP on the scan. Of these twelve patients:

- three presented acutely with seizures, 2 had CSF taps showing ICP levels of 4 and 12 mmHg respectively with no evidence of shunt infection and the third patient had a normal CT scan. All three patients had abnormal EEG recordings and were started on anticonvulsant therapy.
- three presented with intermittent headaches, 2 of them had well controlled hydrocephalus on CT scan and one patient had an overnight sleep ICP recording showing normal mean levels of ICP with no significant periods of spontaneous ICP elevation.

- five patients presented with behaviour changes including lethargy, aggressive or irritable behaviour and lack of developmental progress. Two of them had normal ICP levels measured through their reservoirs and three had CT scans confirming controlled hydrocephalus.
- one patient who also suffered from eczema presented with unsettled and restless sleep. It was difficult to be clinically certain if this was due to his eczema or associated with non-compensated hydrocephalus. CT scan did not reveal any increase in ventricular dilatation and ICP levels measured through his reservoir were within normal limits.

None of these thirty-one patients required revision of shunts for at least six months after the TCD recordings reported.

Results

Figure 5.5 shows the RI values from these 31 symptomatic and asymptomatic patients with functioning shunts plotted against their age. The boxed area shows the normal range (mean \pm 2 sd) for RI values over the age of one year. Figure 5.6 shows the MFV values from these 31 patients plotted against their ages with the normal mean \pm 2 sd MFV values for the corresponding age groups. The mean (\pm sd) RI from these 31 patients was 0.55 (.06) while mean (\pm sd) RI in normal controls was 0.54 (.03). Ten of the functioning-shunt patients were under one year of age. Because of the difference in normal values of CBFV indices in young infants compared to older children and as the study 'normal' group only contains children over the age of one year, only CBFV values from children in the functioning-shunt group over 1 year of age (n = 21) were statistically compared to the normal control group by unpaired t-test.

The mean RI (sd) in the 21 children with functioning shunts over one year old was 0.53 (.06) while the mean (sd) RI in normal controls was 0.54 (.03). The mean (sd) MFV in these children was 78.5 (21) cm/sec while the mean MFV in the normal controls was 83.8 (15) cm/sec. There were no statistically significant differences for RI, MFV, PSV and EDV values between these 21 patients with functioning-shunts and the normal children. There was also little difference in RI and MFV values between the symptomatic or asymptomatic patients. As previously reported from the study of CBFV changes before and after shunting, the mean (sd) RI

values in the Group II patients (>1 year of age) prior to shunting was 0.67 (.06), decreasing to 0.55 (.05) after successful shunting. Thus as would be expected, the RI values of these 31 children with functioning shunts are similar to the values seen immediately after successful shunting.

5.5.4 Non-progressive ventricular dilatation study

TCD examinations were performed serially on twelve patients with ventricular dilatation who subsequently showed no evidence of progression. Their clinical details and CBFV data from their last TCD examination during the period of assessment are shown in Table 5 (ix) below. These patients had ventricular dilatation but were unshunted, had no clinical signs or symptoms of raised ICP and all these patients subsequently have remained unshunted with stable ventriculomegaly.

Table 5 (ix) Clinical details and CBFV data in patients with non-progressive ventricular dilatation

Patient	Aetiology	Age	RI	MFV (cm/sec)	PSV (cm/sec)	EDV (cm/sec)
C S	post-haemorrhage	2 wk	0.61	56	90	35
ST	congenital	3 wk	0.745	49	86	22
DM	post-haemorrhage (preterm)	5 wk	0.74	23	45	11
NB	occipital encephalocoele	6 mth	0.70	55	94	28
DS	congenital	6 mth	0.60	72	109	42
DP	congenital	6 mth	0.67	79	129	42
FR	post-haemorrhage	9 mth	0.59	78	116	47
JB	preterm	13 mth	0.53	70	102	47
DB	idiopathic	3 yr	0.53	48	68	31
CMcM	post-haemorrhage	3.9 yr	0.56	94	70	62
RMcL	post fossa cyst	11.9 yr	0.45	111	161	87
VH	post-traumatic	14.3 yr	0.56	105	165	71

5.5.4(a) CBFV data in patients with non-progressive ventricular dilatation

CBFV data from the children aged >12 months with non-progressive ventricular dilatation show that their RI values were within normal

range. RI values from the young infants (less than 3 months) were no greater than 0.75 and in the older infants RI values were no greater than 0.7 which were within reported normal ranges for neonatal infants (Chaddock & Seibert 1989). MFV values were slightly lower than normal range in one child (DB) and slightly greater than normal range in 2 of the older children (RMcL, VH).

There are not well-established normal ranges for post-neonatal infants in the literature, particularly for RI values. It is often difficult for practical reasons to obtain reliable normal data in this age group as normal infants at this age are often fairly lively or easily inclined to cry when a TCD probe with cold ultrasound gel is placed against their head. Thus it can be difficult to be very certain of mild to moderately elevated RI values within this age group. Bode and Wais (1988) have reported the RI to show a steady gradual decline over the first year of life from a mean value of 0.7 to a mean value of 0.55 and remaining fairly steady thereafter. The RI values from these infants show a similar pattern and were within reported upper limits for term infants. One patient, aged 6 months (NB) had an RI value at the upper limit of normal for his age. He was closely followed up and showed no further increase in RI while remaining clinically stable with his head circumference measurements increasing at a normal rate.

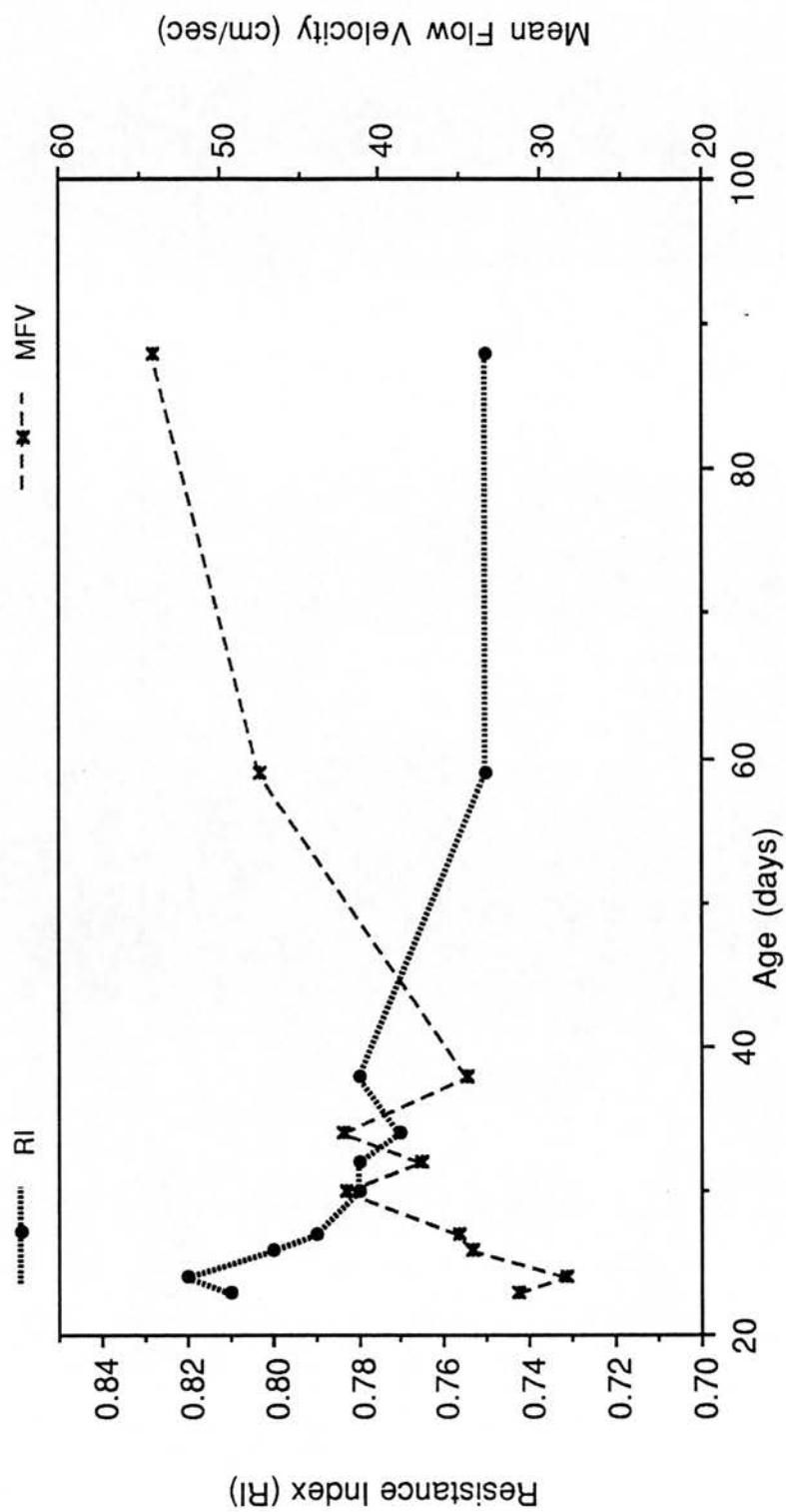
5.5.4 (b) Case illustrations -

Case 1: Patient FR was born at 35 weeks gestation by uncomplicated spontaneous vaginal delivery with a birth weight of 2.55 kg. Apgar scores following delivery were good. However, irritability was noted on day 3 and cerebral ultrasonography detected intraventricular haemorrhage on the right involving periventricular areas. Communicating ventricular dilatation was noted on subsequent scans, right side more than left. At lumbar puncture performed on day 9 opening CSF pressure was 8 mmHg. His head circumference was on the 90th centile for age. Over the first two weeks there was further increase in ventricular dilatation with new cystic changes noted on ultrasonography. CSF pressure measured at lumbar puncture on days 9 and 13 were between 6 to 8 mmHg. On day 23, his opening CSF pressure was 10 mmHg and at pre-tap TCD examination the RI was 0.84. Ten mls of CSF was drained for therapeutic reasons, the CSF

pressure decreased to 2.5 mmHg and the RI to 0.63 post-tap. Subsequently he remained clinically stable with no further progressive increase in ventricular dilatation. Head circumference measurements over the first two to four weeks had increased from the 90th to the 97th centile, then settling back to remain on the 90th centile. Serial CBFV values from bedside measurement in quiet conditions over the first three months are shown in Figure 5. 7. His RI value at 9 months of age was 0.59.

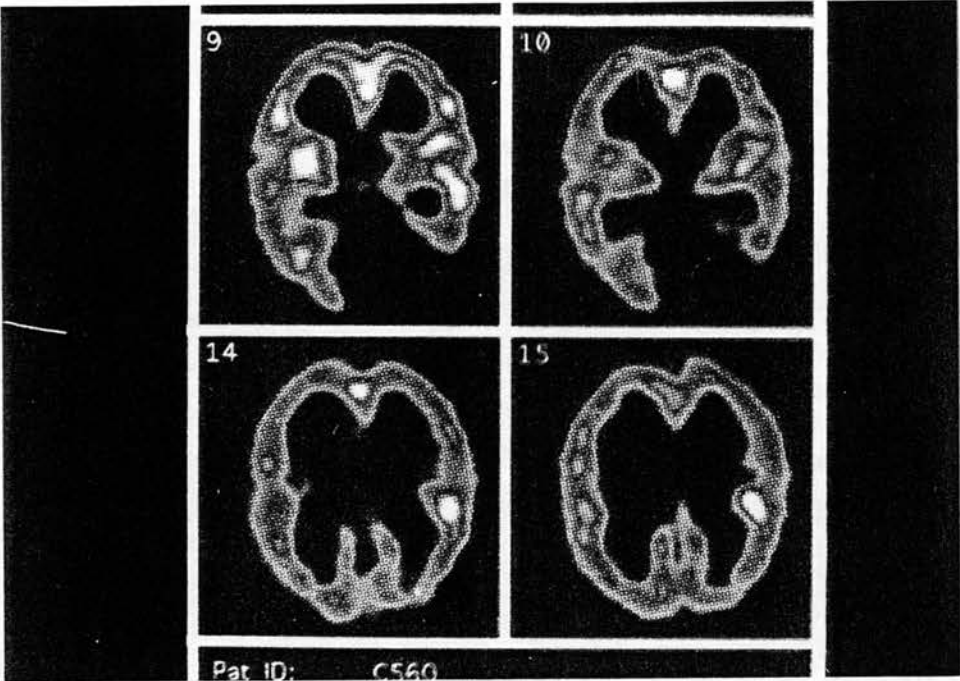
The last ultrasound scan at the age of 22 months showed persistent ventricular dilatation, right more than left with a right porencephalic cyst. He showed developing clinical signs of a left hemiplegia from the age of two months, which was most likely the sequelae of the initial haemorrhage with involvement of the periventricular region. At his most recent review at the age of 32 months he has a mild left hemiplegia with no significant cognitive delay, no signs or symptoms of raised ICP, and his hydrocephalus remains clinically 'arrested' without a shunt. Serial RI values in the early period of assessment for this patient were helpful in suggesting that over the period of assessment the hydrocephalic process appeared to be gradually compensating without progressive increase in ICP or evidence of cerebrohaemodynamic compromise. As a result we were able, with greater confidence, to avoid shunting this patient and he remains stable without the longterm complications of ventricular shunts.

Figure 5.7 : serial RI and MFV values from patient FR with non-progressive ventricular dilatation, remaining unshunted.



Case 2: Patient RMcL was seen at the age of 12 years following a possible seizure episode. His CT scan showed significantly dilated lateral and third ventricles with a large subarachnoid cyst in the posterior fossa. He had previously been followed up in infancy with arrested hydrocephalus and ataxic diplegia. ICP monitoring overnight through a frontal reservoir showed mean ICP levels between 14 - 16 mmHg with no significant periods of spontaneous ICP elevation. His mean RI value from TCD examination was 0.45. Thus his hydrocephalus, from ICP and TCD studies, appeared to be well compensated and he remained unshunted. At outpatient review he has remained clinically stable, his most recent mean RI value was 0.5. He had repeat CT scans which have shown no significant change in the size of the ventricles or the subarachnoid cyst. He has also had a SPECT scan (Figure 5. 8) showing normal symmetrical uptake into cortical areas not directly affected by the posterior fossa lesion. This indicates that although he remains unshunted and his ventricles and posterior fossa cyst are significantly dilated, his cerebral perfusion is nevertheless uncompromised, as suggested by non-invasive TCD measurements

Figure 5.8: SPECT scan of patient RMcL with arrested hydrocephalus showing symetrical uptake into cortical areas not directly affected by the posterior fossa subarachnoid cyst.



5.5.5 Volume-flow velocity response (VFR) study

Single measurements of ICP, even when repeated on separate occasions do not provide any information on intracranial dynamics and compliance to separate those who may have reached a critical point with limited available volume buffering capacity. The Pressure-Volume Index (PVI) and the Volume-Pressure Response (VPR) described by Marmarou et al (1975) and Miller (1975) respectively provide an estimate of intracranial compliance by using volume challenge techniques. As there is a consistent relationship between RI and ICP, particularly in individual patients, this CBFV index may theoretically also have an exponential relationship to changes in intracranial volume. Investigation of a direct CBFV response to volume changes in hydrocephalic patients, i.e. a volume-flow velocity response (VFR), could thus enable us to directly examine the cerebrohaemodynamic response and allow estimation of a residual volume buffering capacity rather than to infer haemodynamic changes from the resultant CPP change. Serial VFRs theoretically then could help to indicate if progression or arrest of the hydrocephalic process is occurring depending on the change in this 'volume-buffering' capacity. There have been no previous reports on sequential CBFV change with volume manipulation in hydrocephalic children.

Eighteen patients with hydrocephalus of varying aetiology were studied. Their clinical details are listed in Table 5 (x). A total of 58 CSF taps were carried out with sequential CSF volume drainage and simultaneous Doppler recordings throughout the procedure. CSF was drained incrementally through a frontal reservoir while Doppler recordings were taken from the ipsilateral temporal position, as previously described (see Figure 3.4). Subsequently the Doppler recordings were played back to measure the change in RI with incremental CSF volume drainage for each tap individually. Ten infants, all of whom were under 3 months of age except for one 8 month old girl, were studied prior to their first ventriculo-peritoneal shunt operation - Group 1. Four of these infants had a number of VFR studies performed while their need for a ventricular shunt was being assessed by consideration of their clinical state, measurements of head circumference, ventricular dilatation and ICP levels. Five patients, aged between 13 months to 10 years 2 months were already shunted and were studied because they presented with symptoms

suggesting raised ICP due to poor shunt function or inadequate compensation - Group 2. Three patients, aged between 3 weeks to 14 years 3 months old have remained unshunted with arrested hydrocephalus - Group 3.

Plots of RI (y) against volume drained (x) from each individual tap were fitted to an exponential curve: $y = a + be^{cx}$ (Figure 5.9)

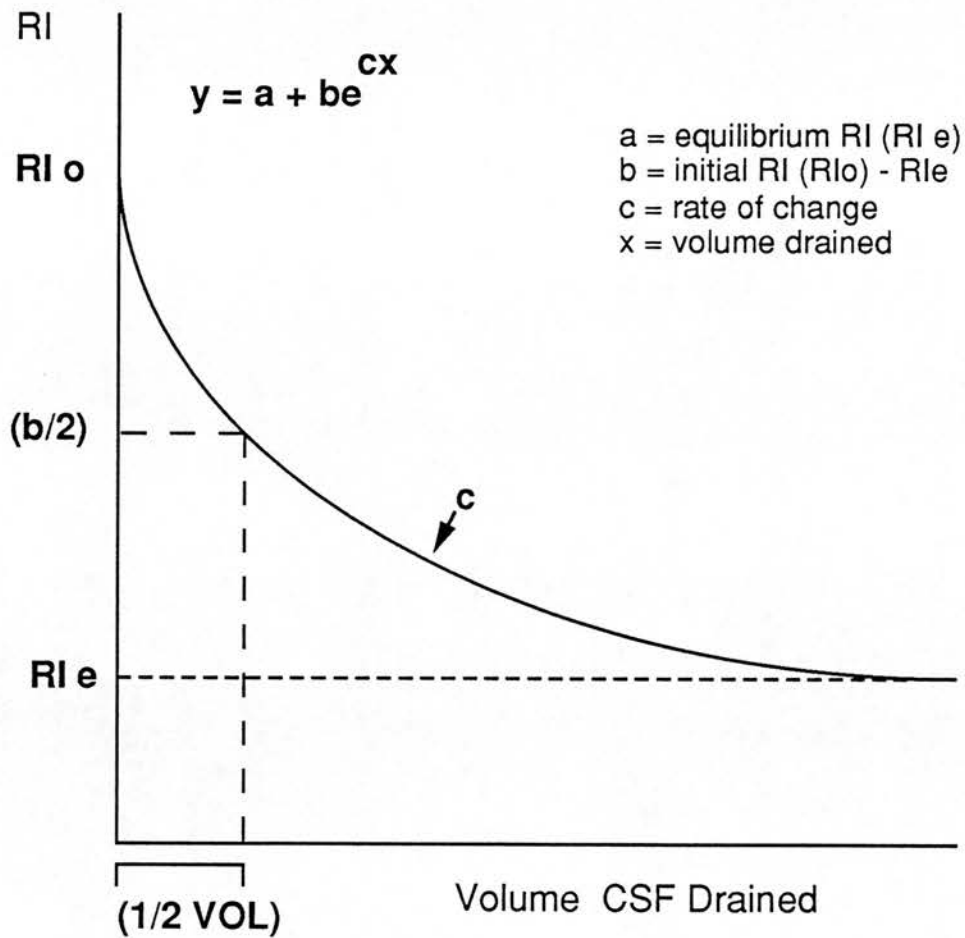
where a = equilibrium RI (RI_e),
 $a + b$ = initial RI (RI_o)
 b = change in RI (RI_o - RI_e)
 c = rate of exponential decay.

A 'half-volume' when half the change in RI had occurred was obtained by calculation, i.e. half-volume = $-0.7/c$.

Table 5 (x) Clinical details and Volume - flow velocity response (VFR) values

Patient (age)	Aetiology of hydrocephalus	half-volume (mls)	R _{Io}	R _{Ie}	opening ICP (mmHg)
<u>Group 1</u> (prior to 1st shunt)					
LF	perinatal infection	0.30	0.76	0.69	8
MG	congenital X-linked	0.70	0.70	0.64	7
JMcC	m-meningocoele	0.27	0.73	0.67	20
NA	m-meningocoele	1.29	0.73	0.61	9
SG	m-meningocoele	2.58	0.69	0.63	13
RA	congenital	0.67	0.84	0.71	12
MR	m-meningocoele	0.53	0.75	0.64	18
CM	m-meningocoele	1.85	0.83	0.70	12
SG (2.5 m)	aqueduct stenosis	0.62	0.76	0.60	10
JC (8 m)	aqueduct stenosis	1.16	0.64	0.55	11
<u>Group 2</u> (previously shunted patients)					
IF (16 m)	post-haemorrhagic	1.3	0.65	0.50	17
PB (13m)	m-meningocoele	3.3	0.62	0.53	17
SH (6y 1m)	post-haemorrhagic	0.75	0.69	0.62	17
CJ (4yr)	post-haemorrhagic	1.25	0.69	0.57	20
LH (10yr)	post-meningitic	2.65	0.48	0.33	11
<u>Group 3</u> (patients remaining unshunted)					
FR (1m)	post-haemorrhagic	3.64	0.82	0.57	10
CMcM (18m)	post-haemorrhagic	11.9	0.62	0.47	16
VH (14 yr)	post-traumatic	4.73	0.57	0.52	13

Figure 5.9 : theoretical exponential curve for prediction of RI change against CSF volume drained.



[1/2 VOL = volume when $RI = RI e + (RI o - RI e) / 2$]

Sequential Doppler data was available from 58 taps. In all but 5 of these taps the decline in RI with incremental CSF volume drained could be fitted against this exponential curve. The initial RI (RIo), equilibrium RI (RIe), the rate of decay and half-volumes could thus be estimated from this model in these 53 taps. Table 5 (x) also shows the RIo, RIe, 'half-volume', opening ICP from these patients; in 5 patients who had more than one VFR study performed only the values from the last study are shown. The 'half-volumes' in the Groups 1 and 2 patients who required new shunts or revision of shunting were smaller than in the Group 3 patients. The mean 'half-volumes' in Groups 1, 2, and 3 were 1.0 (0.7), 2.1 (1.0), and 6.8 (4.5) respectively i.e. a smaller volume of CSF removal was required to obtain half the observed decrease in RI in the Groups 1 and 2 patients compared to the Group 3 patients. All the patients requiring revision/shunting had half-volumes <3.5 mls while the unshunted patients had 'half-volumes' >3.5 mls. There were, however, no statistically significant difference between the half-volumes in the Group 1 and 2 patients compared to the three unshunted Group 3 patients but this may be due to the small numbers of patients.

Figure 5.10 shows the sequential parallel decrease in RI and ICP with CSF volume depletion from patient CMcM who remained unshunted, but clinically stable with significantly dilated ventricles. Figure 5.11 is a plot of observed and predicted RIs with volume depletion from this patient who showed the slowest rate of exponential decay, ie the largest 'half-volume' - 11.9 mls. Figures 5.12 and 5.13 show plots of observed and predicted RIs from two other patients demonstrating a more rapid rate of exponential decay with smaller 'half-volumes'; Figure 5.12 from a neonatal patient who required shunting and Figure 5.13 from a child with a broken shunt requiring replacement.

One of the patients who remained unshunted (VH) with post-traumatic hydrocephalus had two VFR studies performed, the first during the acute stage when she had more marked symptoms of confusion, with moderate cognitive and memory problems, mild unsteadiness and her CT scan had showed a moderate communicating hydrocephalus with a small increase in ventricular dilatation compared to an earlier scan. The second VFR study was repeated when there was an improvement in her confusional

state but persistent problems with concentration, memory and personality change. At her first VFR study the half-volume was 2.22 mls; the second 'half-volume' from her repeat study when her clinical symptoms had improved was 4.73 mls with a slight decrease seen in the opening ICP levels, RIo and RIe levels . Her repeat CT scan showed no further change in the degree of ventricular dilatation.

Figure 5.10 : simultaneous sequential RI and ICP values during a ventricular tap.

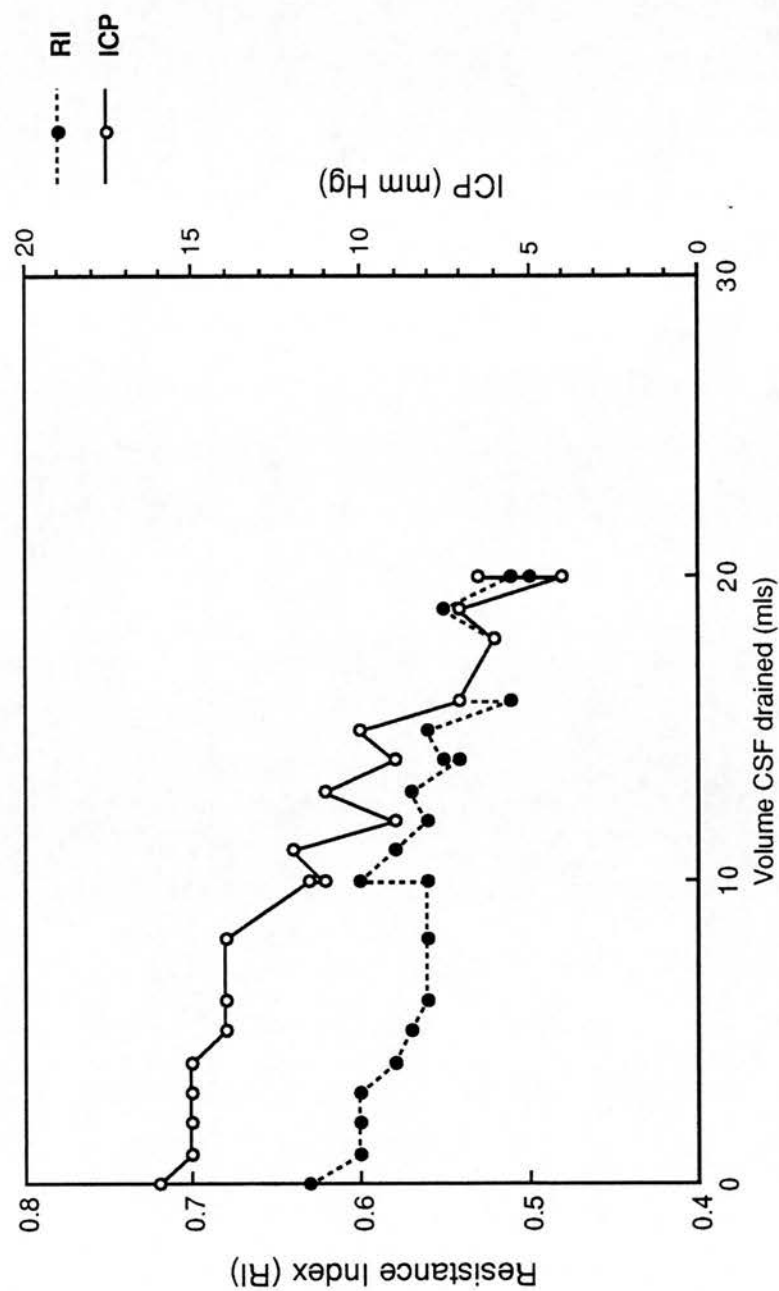


Figure 5.11: observed and predicted RI values against CSF volume drained in patient CMcM (arrested hydrocephalus - unshunted)

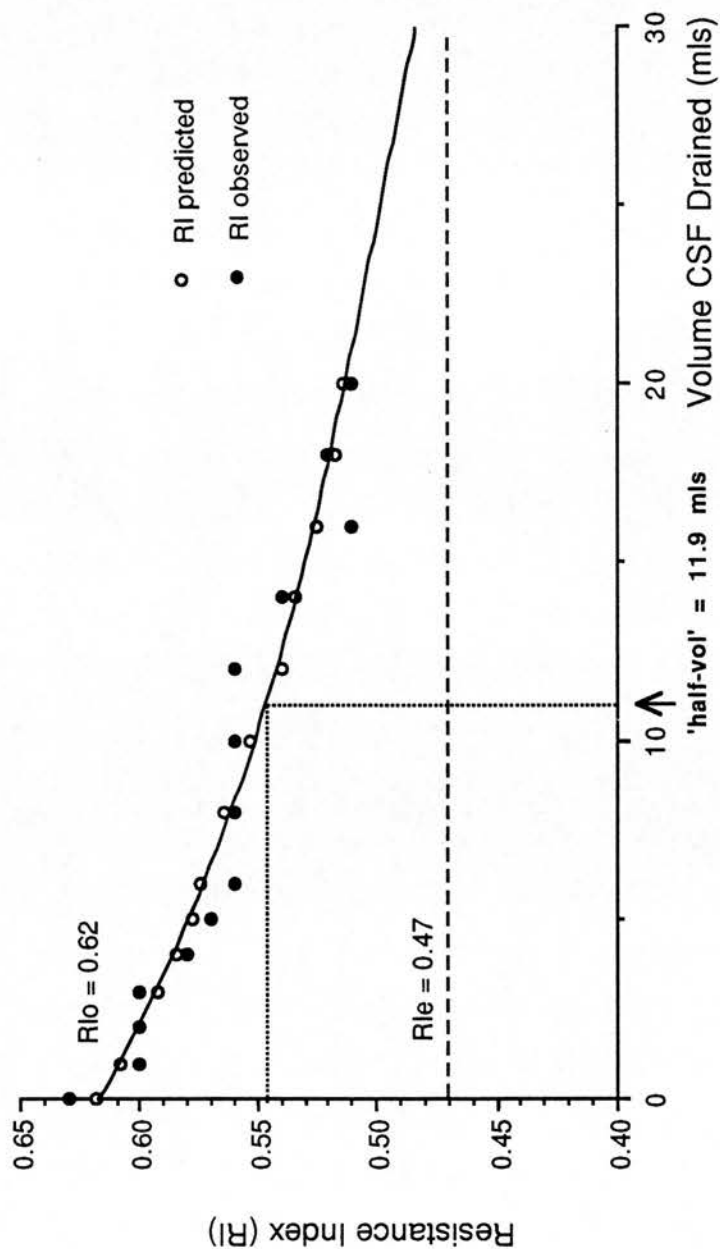


Figure 5.12 : observed and predicted RI values against CSF volume drained from a neonatal patient who required shunting

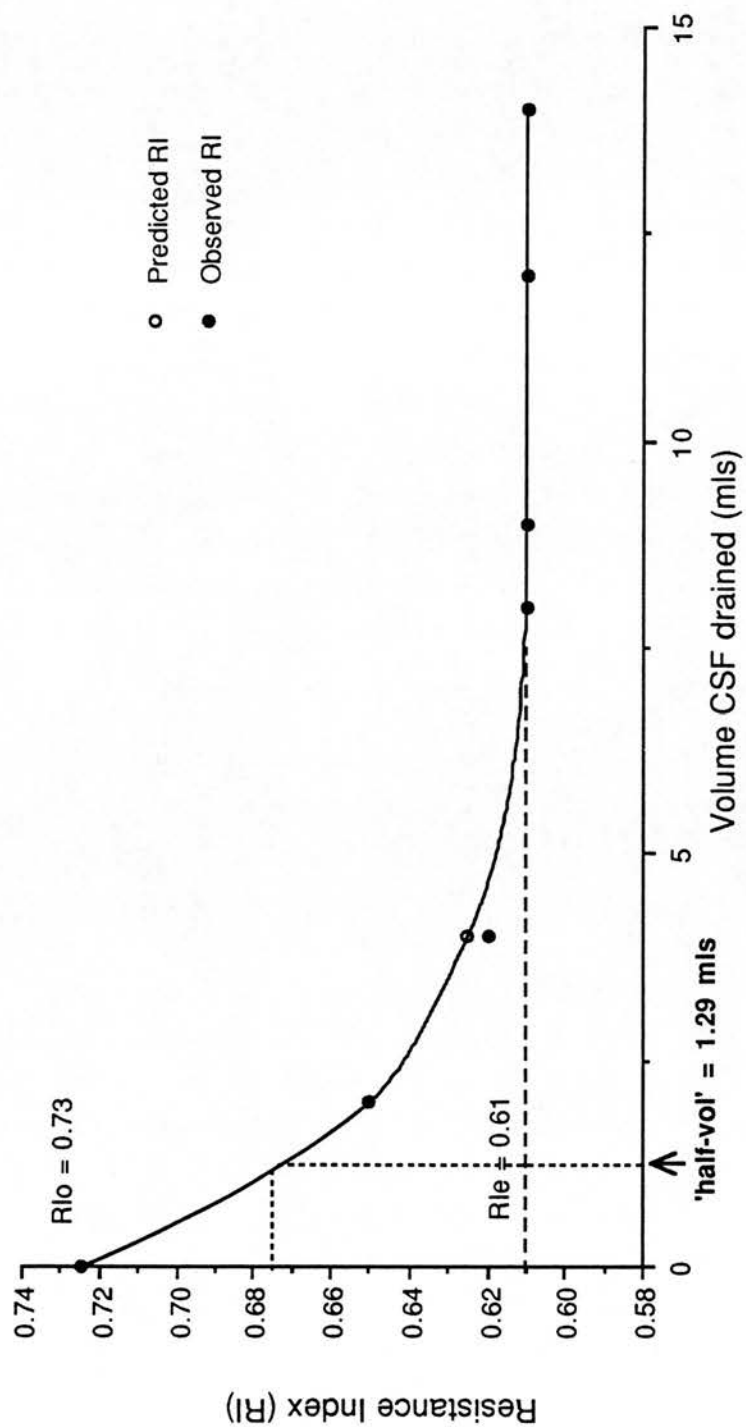
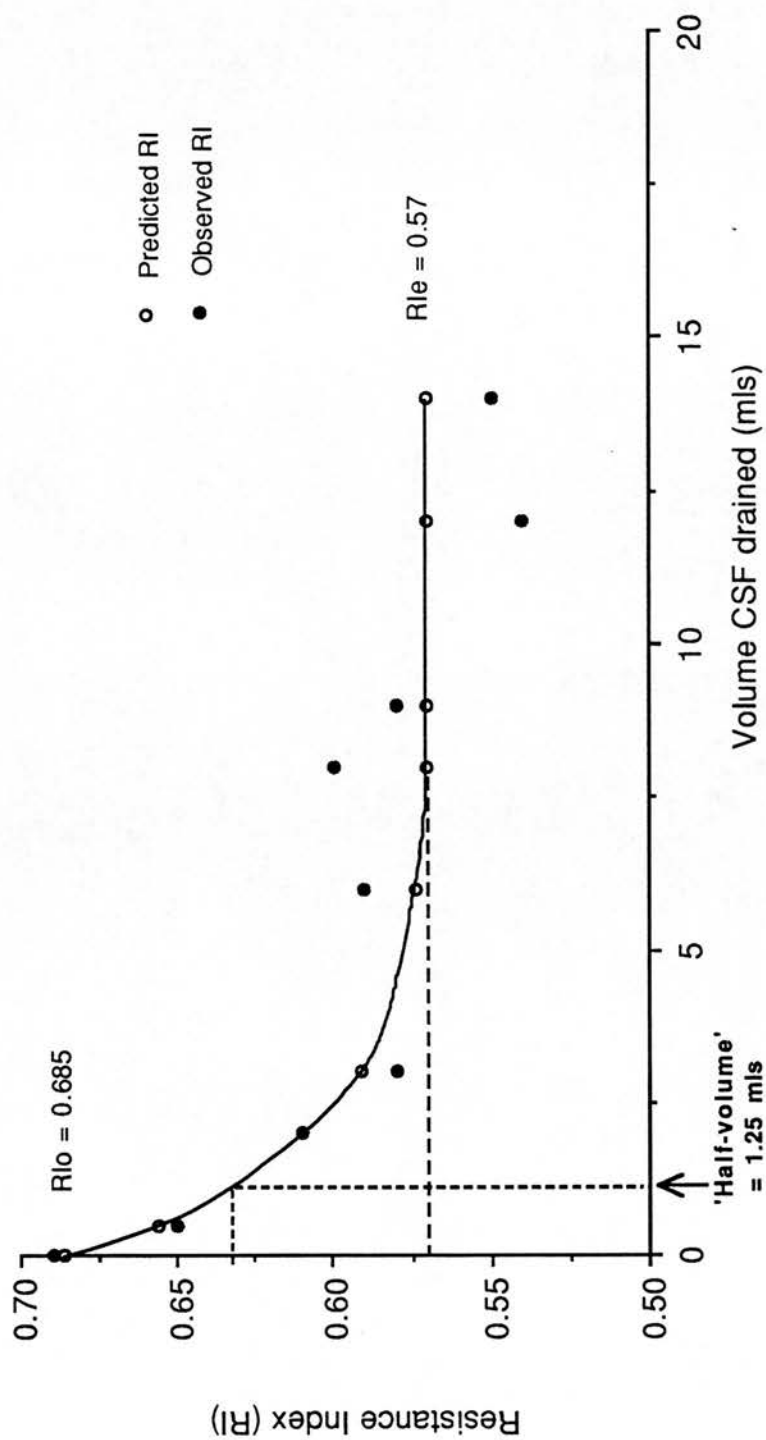


Figure 5.13 : observed and predicted RI values against CSF volume drained from a 4 year old child with a broken shunt



5.5.6 Simultaneous CBFV and ICP variation during sleep study

The aim of the sleep study was to assess the cerebrohaemodynamic response to ICP increase in hydrocephalic children when there was clinical suspicion of reduced intracranial compliance or decompensation of their hydrocephalic state. Eight sleep studies were performed in seven patients, age range 12 - 118 months. Their clinical details are listed in Table 5 (xi). All but one patient (no. 5) had pre-existing shunts. Four patients had no symptoms of raised ICP (case nos. 4, 5, 6, 7) and sleep recordings were performed to assess decompensation because of persistent or increase in ventricular dilatation from neuroimaging. The three patients who were symptomatic (no. 1 - intermittent headaches, no. 2 - deteriorating ataxic gait, no. 3 - irritability and vomiting) had slit-like lateral ventricles on CT scan and normal ICP levels on brief awake ICP measurements. One of them (no. 3) had a repeat study performed after a skull morcellation procedure.

ICP and CBFV monitoring

ICP was continuously monitored through the reservoir and charted by a pen recorder as described earlier. ICP recordings of a total duration of 39.17 hours (mean duration 4.90 hrs, range 1.65 - 8.5 hours) were obtained. The only ICP measurements used in analysis were those that were spontaneous and any due to physiological stress (eg. coughing, movement, etc with an expected raised central venous pressure) were excluded from analysis.

'Stable periods' were defined as periods of unchanging mean ICP levels and 'unstable periods' were those which included plateau and other abnormal waveforms or elevations of ICP which occurred spontaneously and did not include artefactual elevations such as those due to coughing. The mean ICP values over the periods of stable and unstable pressure levels were obtained from review of the charted paper records. Mean basal ICP levels were calculated from 2 - 4 epochs of stable ICP states. The duration of unstable pressure periods was measured and the sum of these unstable periods was then calculated as a percentage of the total ICP recording for each individual study. The maximum mean ICP level during each unstable epoch was also obtained and the type of pressure

elevations i.e. plateau (A), B or C intracranial pressure waves were characterised.

Doppler recordings, as previously described, were made during stable and unstable ICP periods. When it was possible to do so without disturbing the children's sleep, blood pressure was intermittently measured using the oscillometric method with a Dinamap machine. The simultaneous ICP, blood pressure data were voiced over onto the tape. The cerebral perfusion pressure ($CPP = MAP - ICP$) was arithmetically calculated. Graphical plots of simultaneous ICP, CPP MAP and CBFV changes over time were made for each individual study. Linear regression of CBFV indices with ICP were assessed.

Table 5 (xii) summarises the duration and mean ICP during stable (basal) and unstable (with intermittent ICP elevation) periods of each sleep recording. Basal ICP levels ranged between 4.4 - 17.5 mmHg and in 6 of the 8 studies there were unstable periods of intermittent ICP elevation between 20 - 56 % of the individual total period of ICP recording. Table 5 (xiii) summarises the duration of simultaneous ICP/CBFV recording and the correlations between ICP with MFV and RI in individual studies. From the graphical plots of simultaneous ICP/CPP/RI/MFV changes there were mainly two patterns of MFV response observed in association with episodic increased ICP during sleep.

5. 5. 7(a) Decreased MFV response to ICP elevation (Type I)

In four studies, increased ICP was associated with an overall progressive decrease in MFV ($r = - 0.44$, $p < .001$; Figure 5.14) and increase in RI ($r = + 0.64$, $p < .001$; Figure 5.15) which will be referred to as a Type I response. In this group MFV decreased as CPP decreased (overall correlation: $r = + 0.44$, $p < 0.001$). In three of these patients who were symptomatic, chronic CSF overdrainage with slit-ventricle syndrome was suspected. Figure 5.16 shows a graphical plot of simultaneous ICP/CPP/MFV/RI change during the sleep recording in patient no. 1 which illustrates the decreased MFV response associated with an increased ICP and decreased CPP. Plateau (A) or B intracranial pressure waves were recorded in these three patients. Figure 5.17 is a graphical plot of a plateau wave illustrating the marked decrease in MFV associated with reduced CPP to 30 mmHg during the

sustained rise in ICP. With onset of the rapid ICP rise there was a steadily decreasing MFV with increasing RI as ICP increased and the trend reversing as ICP fell. A similar response was also observed during B waves. The fourth patient with mildly increased ventricular dilatation who showed a less marked *decreased MFV response* was thought to have deteriorating shunt function.

Bilateral temporal decompression procedures (which involve removal of the calvarial side of the temporal bones) were performed on patients nos. 1 and 2 and a skull morcellation procedure (removal of cranial sutures and repositioning of morcellated skull bones) on patient no. 3 to enhance intracranial vault volume in the three patients with slit ventricles as overnight ICP monitoring suggested limited intracranial compliance. Skull morcellation procedure can be performed only on young patients, usually up to a maximum age of three years. Shunt revision was performed on the fourth patient.

Table 5 (xi) Clinical details of patients in sleep study

Case No	Sex	Age (mths)	Clinical details	Indication for ICP monitoring
1.	M	108	myelomeningocele, shunted at birth. CT scan: slit lateral ventricles, isolated 4th ventricle	intermittent headaches
2.	F	118	post neonatal coliform meningitis, shunted. CT scan: slit lateral ventricles, isolated 4th ventricle	deteriorating ataxic gait
3.	F	25	posthaemorrhagic, shunted aged 6 wks. Secondary craniosynostosis, 1st skull morcellation aged 12 mths, marked developmental delay. CT scan: slit lateral ventricles	irritability & vomiting. ICP when awake - 6 mmHg
4.	M	37	postpneumococcal meningitis, shunted aged 3 mths. Deafness, seizures, global developmental delay.	CT scan: increased ventricular dilatation
5.	M	14	posthaemorrhagic, <u>unshunted</u> . Asymptomatic, mild delay in gross motor development	CT scan: persistent ventricular dilatation
6.	M	34	posterior fossa arachnoid cyst, cyst-peritoneal shunt aged 6 months. Asymptomatic, normal development	CT scan: persistent ventricular dilatation
7.	M	12	myelomeningocele, shunted aged 2 wks. Asymptomatic.	CT scan: mildly increased ventricular dilatation

Table 5 (xii) Mean ICP during Stable (basal) and Unstable periods of individual sleep records

Case No.	Duration ICP Record (hours)	Mean basal ICP (mmHg)	No. of Unstable Periods	Duration Unstable Periods (hours)	(% Total ICP Recording)	Mean Maximum ICP During Unstable Period (mmHg)	Type of Intermittent Pressure Elevations
1	8.5	4.4	5	3.29	(39.0%)	33.4	20 mins. plateau wave to mean 58 mmHg, B& C waves
2	2.2	9.0	3	0.54	(24.5%)	32.3	B waves
3 pre-op	1.65	17.5	3	0.71	(42.7%)	33.5	B waves & intermittent elevation to 30 - 35 mmHg for 10 - 15 mins.
3 post-op	4.25	16.7	1	0.25	(6.0%)	24.3	small C waves
4	3.88	14.7	3	0.79	(20.2%)	31.3	intermittent rise to mean max 28 - 30 mmHg for 5 - 6 mins.
5	5.09	10.5	5	1.86	(36.7%)	21.5	intermittent rise to mean max 19 - 25 mmHg for 6 - 10 mins.
6	7.7	16.4	2	0.55	(7.0%)	24.0	intermittent rise to mean max 24 mmHg for 4 - 15 mins.
7	5.9	15.2	6	3.31	(56.0%)	31.2	intermittent rise to mean max 25 - 30 mmHg for 10 - 20 mins.

Table 5 (xiii) Correlation (r) between ICP and Doppler indices in individual sleep records

Case No.	Duration CBFV Record (hours)	<u>ICP/MFV</u>		<u>MFV/PSV</u>		<u>MFV/EDV</u>		<u>ICP/RI</u>	
		r	p	r		r		r	p
1	5.17	-0.64	<.001	+0.57		+0.96		+0.89	<.001
2	0.71	-0.46	<.05	+0.68		+0.95		+0.7	<.001
3 pre-op	1.61	-0.24	ns	+0.78		+0.92		+0.61	<.001
4	3.75	-0.13	ns	+0.77		+0.985		+0.41	<.01
5	4.0	+0.37	<.01	+0.96		+0.93		+0.69	<.001
6	2.45	+0.64	<.001	+0.86		+0.94		+0.13	ns
7	3.5	+0.63	<.001	+0.91		+0.96		-0.8	<.001
3 post-op	5.25	+0.58	<.001	+0.72		+0.80		+0.03	ns

Figure 5.14: MFV / ICP correlation in 4 sleep studies showing decreased MFV response to ICP rise (Type I response)

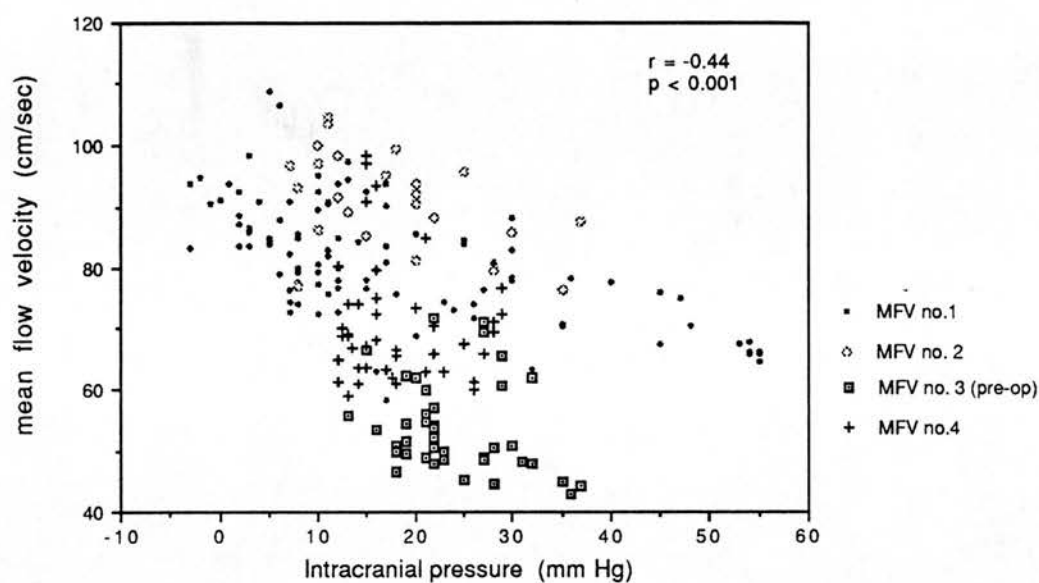


Figure 5.15 : RI / ICP correlation in 4 sleep studies showing increased RI with ICP rise (Type I response)

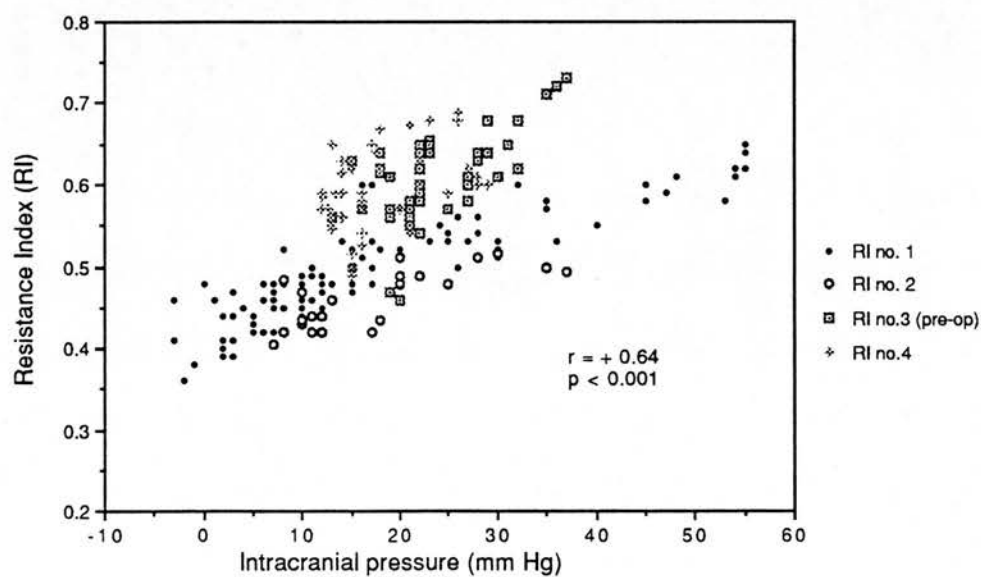


Figure 5.16: graph of simultaneous ICP, CPP, MFV and RI values from patient no.1 which illustrates a decreased MFV response to increase in ICP (Type I). As ICP increases, CPP and MFV decrease while RI increases.

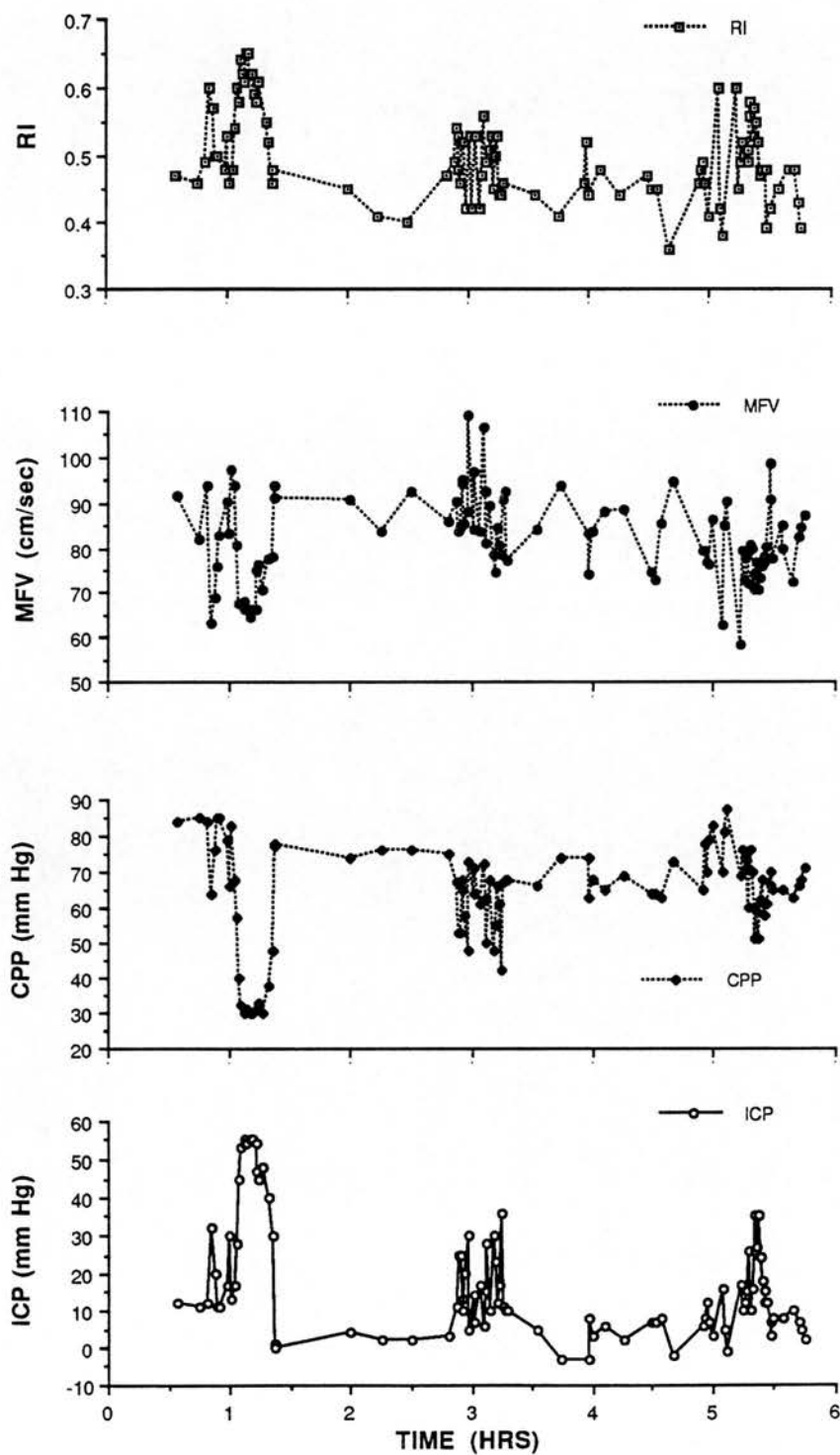
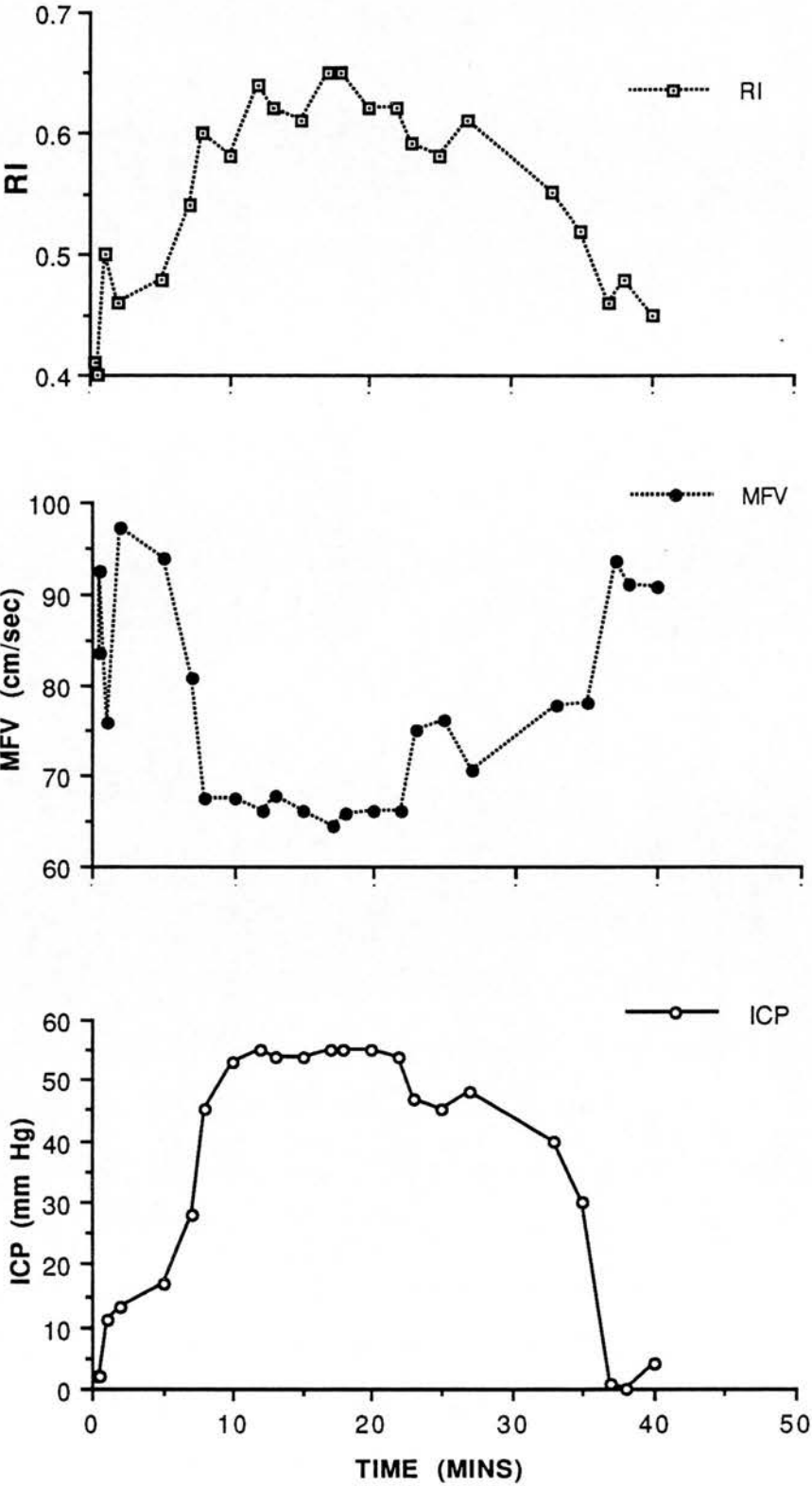


Figure 5.17: graph of ICP, MFV and RI during a plateau wave showing the marked decrease in MFV and rise in RI with the precipitate increase in ICP, the trend reversing with the fall in ICP.



5. 5. 7. (b) Increased MFV response to ICP elevation (Type II)

Another pattern of CBFV response with corresponding increased MFV when ICP increased ($r = + 0.65$, $p < .001$; Figure 5.18) which will be referred to as a Type II response was observed from graphical plots in the other 4 studies. CPP data were available on 3 of these studies. There was an overall increase in MFV as CPP decreased ($r = - 0.46$, $p < 0.001$). Figure 5.19 shows a graphical plot of simultaneous ICP/CPP/MFV/RI from patient no. 5 which illustrates the Type II (*increased MFV*) response during rise in ICP. In three of these studies increased ICP was associated with slight or definite increase in RI while in one patient (no. 7) who also showed an increased MFV response, RI decreased as ICP increased (Figure 5.20). None of these studies with an increased MFV response had sustained plateau (A) or B intracranial pressure waves recorded; the maximum were episodic elevations of 10 - 20 minutes duration rising to a mean maximum pressure of 20 - 30 mmHg, although the overall duration of unstable ICP periods were also a considerable percentage of the total period of ICP recording in patients no. 5 and 7. A repeat study performed following a skull morcellation procedure in patient no. 3 who previously had a Type I (*decreased MFV*) response to increased ICP showed improvement with marked reduction in percentage duration of unstable ICP periods, reduction in mean maximum ICP levels and a change to a Type II (*increased MFV*) response to rise in ICP.

It was likely that patient no. 5 had compensated arrested hydrocephalus as he remained clinically well while unshunted with little clinical evidence of significant ischaemic effect although periods of intermittent ICP elevations were present on his overnight recording. At his most recent follow-up nine months later his head circumference growth remained as before on the 75th centile and he continues to make appropriate developmental progress except for a mild delay in gross motor skills which are more likely to be related to the intraventricular haemorrhage insult from his preterm neonatal period. Patient no. 6 who also showed a Type II (*increased MFV*) response to rise in ICP has also remained clinically asymptomatic with normal developmental achievements for his age. Thus although he has persistent significant ventricular dilatation no further surgical shunt procedure was felt to be necessary.

The relationship between ICP and CBFV indices in hydrocephalic children involves examining not only the CBFV indices in response to changing ICP but also changes in CBFV indices independent of ICP changes. During 'stable' ICP periods there were no marked fluctuations detected in CBFV indices as can be seen from Figures 5.16, 5.19, 5.20.

Plots of MFV against PSV and EDV in each individual study showed that the change in MFV during the Type I (decreased MFV) response was more closely related to change in EDV (range of correlation values, r : 0.92 - 0.985) than to change in PSV (range of correlation values r : 0.57 - 0.78) suggesting that elevation in ICP during these studies caused more significant increase in distal resistance to flow. During the studies with a Type II (increased MFV) response, the change in MFV was equally related to change in EDV (range of correlation values, r : 0.8 - 0.96) as in PSV (range of correlation values, r : 0.72 - 0.96).

Figure 5.18: MFV / ICP correlation in 4 sleep studies
showing increased MFV response to ICP rise (Type II response)

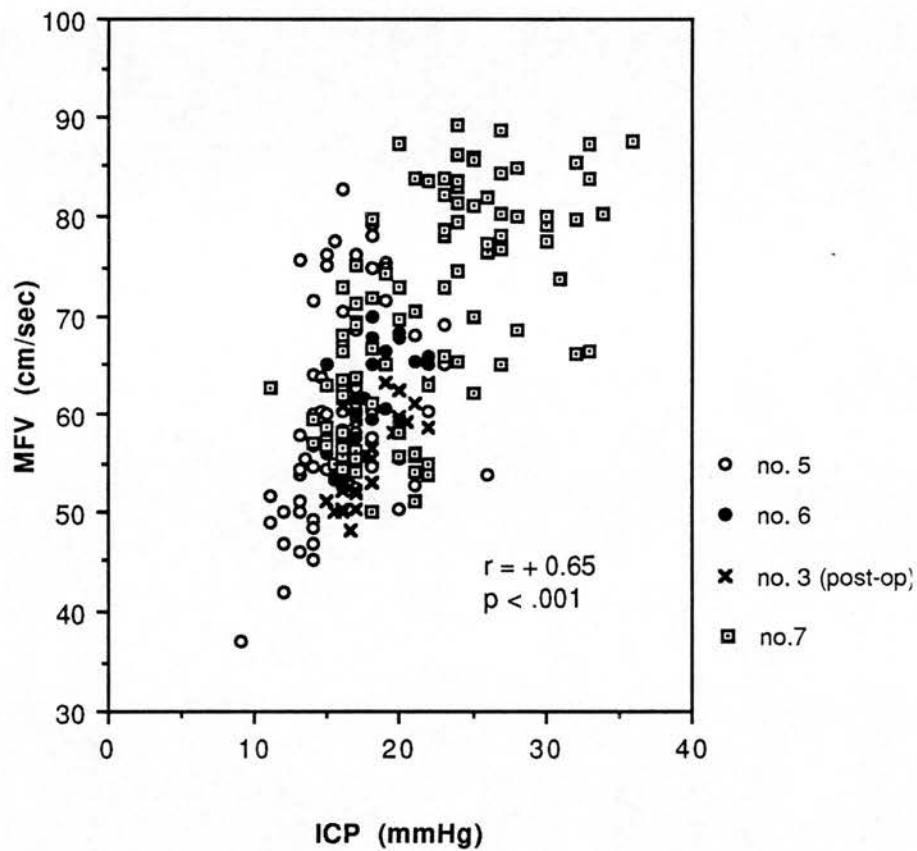


Figure 5.19: graph of simultaneous measurements of ICP, CPP, MFV and RI from patient no.5 which shows an increased MFV response (Type II) to rise in ICP. The RI increased as ICP increased.

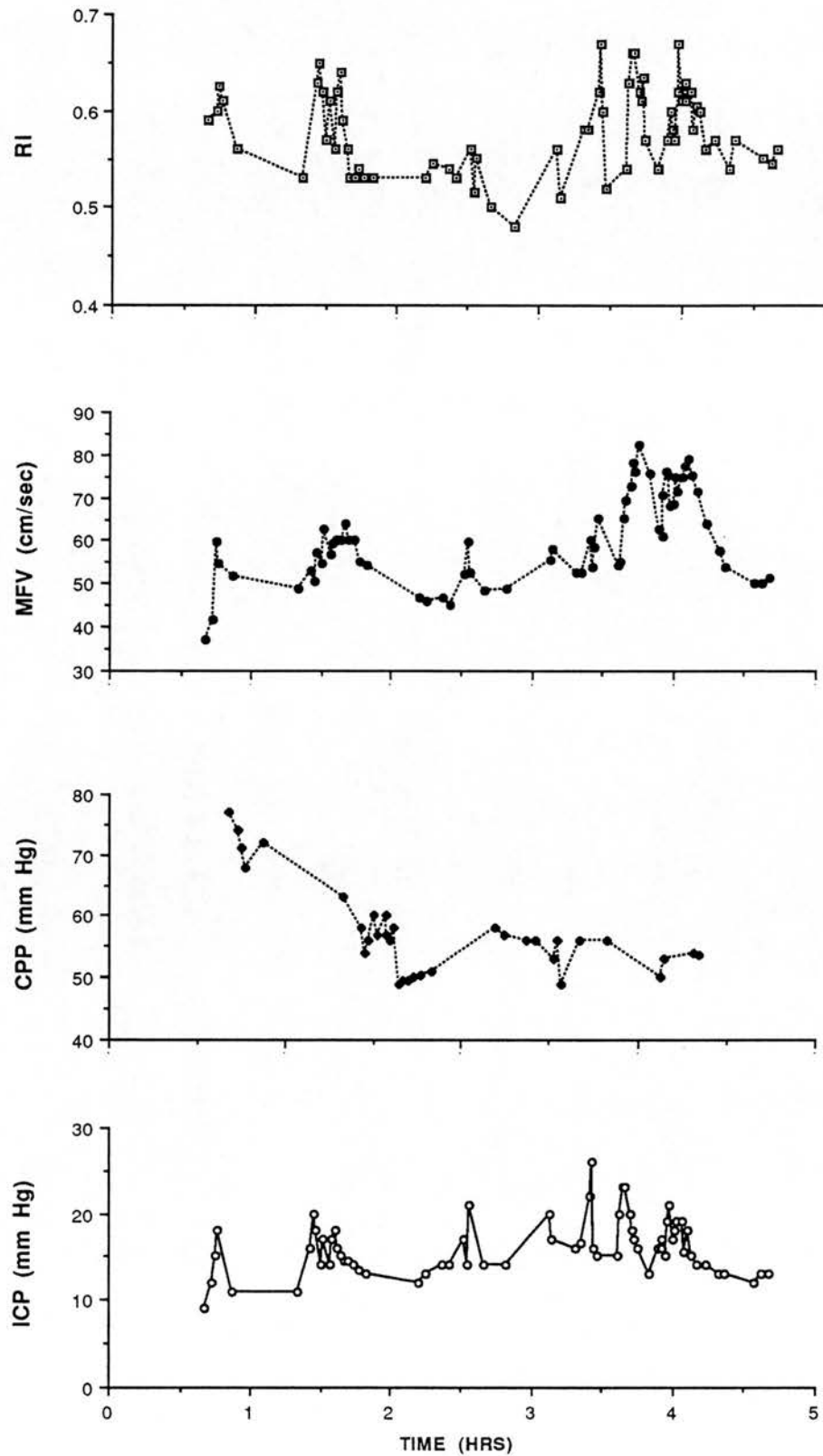
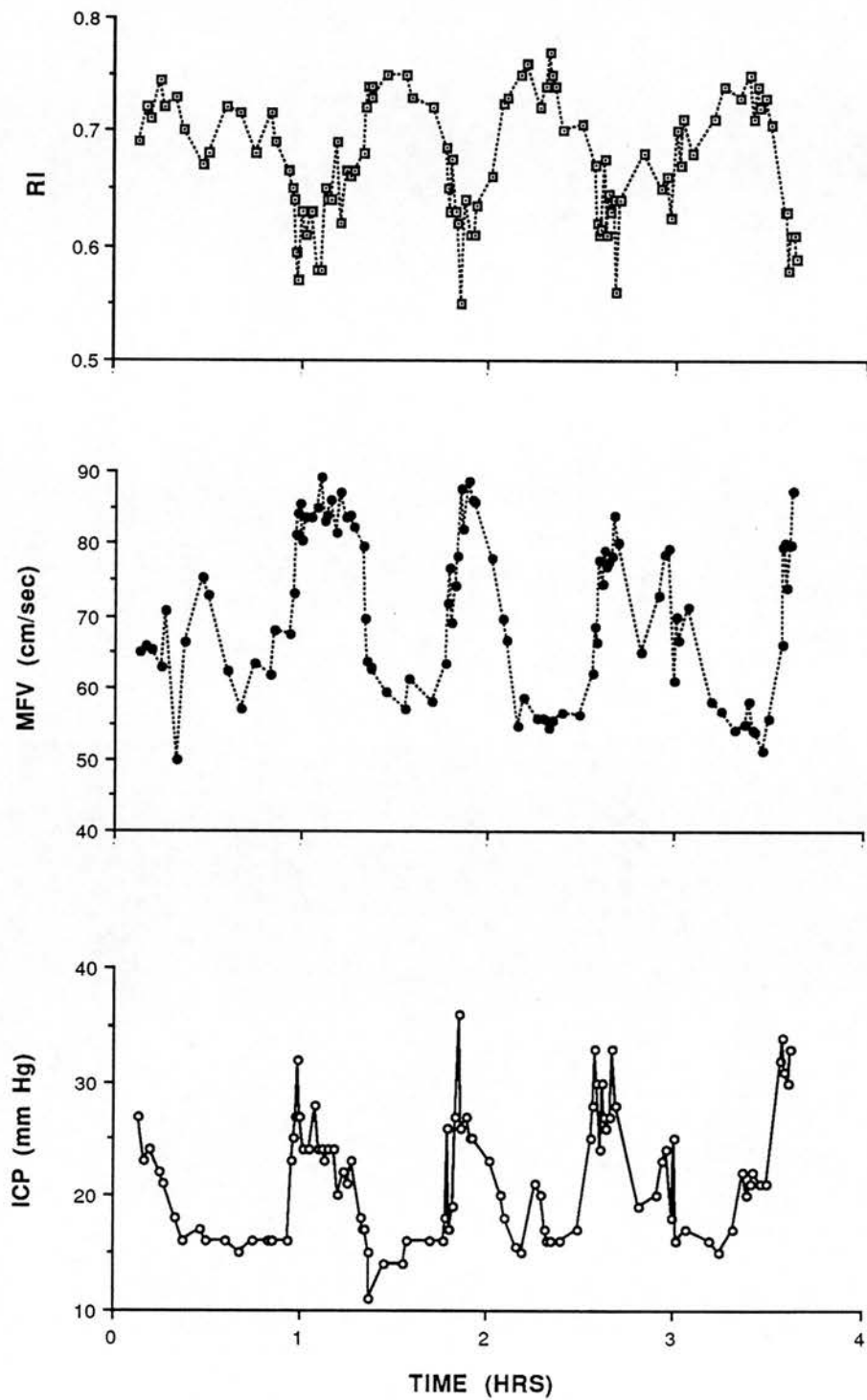


Figure 5.20: graph of simultaneous ICP, MFV and RI values from patient no.7 which shows an increased MFV response (Type II) to rise in ICP. In this patient the RI decreased as ICP increased.



5.6 Discussion

5.6.1 Effect of CSF drainage by ventricular taps on CBFV

There was a consistent and highly significant decrease in RI in all patients after ventricular CSF taps, supporting similar findings in all previous studies which have examined the effect of CSF drainage on waveform pulsatility (Hill & Volpe 1981, Seibert et al 1989, van Bel et al 1988, Nishimaki et al 1991). However, while there has been uniform agreement that pulsatility decreases after CSF drainage the interpretation of the changes seen have differed. Alvisi et al (1985) and van Bel et al (1988) have reported the increased pulsatility in infantile hydrocephalus to be due to an increased PSV and have attributed it to increased cerebrovascular compliance. This study shows that EDV increases significantly after CSF drainage and the fall in RI is thus due to an increase in EDV. More recent studies have also related changes in pulsatility to changes in EDV (Deeg et al 1988, Huang & Chio 1991). The decrease in RI after all taps which was associated with a significant increase in EDV and MFV in this study suggests that distal resistance to flow is reduced when ICP has decreased as a result of CSF drainage. This supports the view that the RI may in this clinical situation be a reliable index of cerebrovascular resistance. The finding of a significantly increased MFV after CSF taps further supports that perfusion is improved as a result of the diminished impedance to flow. However, this was a less consistent and less significant change than the reduction in RI. Absolute velocity values such as the MFV, EDV, PSV are more greatly affected by variation in the angle of insonation. This may be considerable in patients with hydrocephalus when the course of the intracranial vessels can be significantly distorted (Finn et al 1990). As a ratio, the effect of the insonation angle is minimised by the use of the RI and these results support it to be a more reliable index in hydrocephalic patients.

These results show a reliable overall correlation between RI and ICP only in older infants and children. In neonatal or young infants the overall correlation for data taken from the whole group is poor while there remains a highly significant correlation for RI/ICP data in individual patients. Animal experimental data (Seibert et al 1989) and clinical studies reported by Chadduck et al (1991), Pople et al (1991), Hanlo (1990),

Horikawa (1991) have also shown a correlation between increased ICP and increased CBFV waveform pulsatility. Chadduck et al (1991) noted that in the range of RI between 0.45 - 0.60 (i.e. the normal range) the correlation may not be so reliable although beyond these values there is a better correlation. The results in this study for the Group II patients were fairly similar to that described by Chadduck and colleagues (1989, 1991). There is thus overall general agreement from studies in older children with hydrocephalus that there is a reliable relationship between RI and ICP. In contrast Quinn et al (1992) found that while RI decreased significantly after taps there was no correlation between RI and ICP in their three neonatal patients and concluded that while RI may reflect changes in ICP in the acute situation, it was of limited value in prediction of ICP for individual infants with post-haemorrhagic hydrocephalus. This may have been likely because their patients were predominantly premature young infants where there could be considerable variation in the cardiac contribution to the cerebral arterial waveform such as in those with a persistent ductus arteriosus.

None of these previous clinical studies have specifically differentiated between the relationship of ICP and waveform pulsatility in preterm and neonatal infants compared to older infants and children as the study groups have usually been exclusively one or the other group. In older infants and children whose cranial sutures have fused their intracranial dynamics would be expected to be more uniform and thus an overall correlation between RI and ICP in this group is not surprising. However as seen, intersubject comparison of absolute velocity values would be unreliable as there would be considerable variation of the angle of insonation and arterial cross-sectional diameter.

The Group I young infants in this study had established hydrocephalus of mixed aetiology and none had clinical evidence of any significant cardiac condition. However, there was an unreliable overall correlation for intersubject RI / ICP values. This may be because in these young infants the skull is still poorly mineralised with unfused cranial sutures thus allowing a highly variable degree of intracranial and cerebrohaemodynamic compensation in individual cases. Depending on the gestational age, the underlying cause, the rate of progression in ventricular dilatation,

the poorly mineralised cranial bones and unfused sutures may accommodate a highly variable expansion of the head circumference to compensate or 'buffer' against increasing ICP. In some infants the observed ventricular dilatation is associated primarily with atrophic changes as a consequence of ischaemic injury rather than raised ICP. Thus not surprisingly, ventricular size has never been a reliable guide to the level of ICP in young infants.

It is also likely that for each individual young infant with ventricular dilatation a different level of ICP is required to cause significantly compromised cerebral perfusion. Thus some infants who may not have markedly raised levels of ICP can nevertheless have significantly raised levels of cerebrovascular resistance with a greater risk of compromised perfusion. Isolated single measurements of RI are likely though to be of limited value. However, by following individual cerebrohaemodynamic trends, serial RI values may provide a reliable index of distal cerebrovascular resistance associated with raised ICP for each individual patient, as suggested by the correlation between RI and ICP in individual patients. This could be very useful in clinical management especially as there are few other non-invasive methods of assessment of cerebral perfusion available.

As there was little immediate change in ventricular size but highly significant changes in RI and ICP after CSF drainage it strongly suggests that raised RI in hydrocephalic patients is associated with raised ICP rather than ventricular dilatation per se as had been suggested by Hill and Volpe (1981) and Lui et al (1990). This is further supported by these study results showing a reliable correlation between RI and ICP for older infants and children or in individual young infants.

5.6.2 Effect of ventriculo-peritoneal shunting on CBFV

There were very similar changes in CBFV values after ventricular shunting or shunt revision as the changes seen after ventricular CSF taps in both Group I and II patients i.e. decreased RI, increased MFV and EDV values. Mean CBFV indices pre- and post-operatively, even though measured on different days were indeed very similar to the values measured before and after ventricular taps. Deeg et al (1988) reported

similar results where the decrease in pulsatility after shunting was associated with an increase in EDV. All other reports on waveform pulsatility changes after ventricular shunting or revisions of malfunctioning shunts (Chaddock et al 1991, Norelle et al 1989, Lui et al 1990, Horikawa 1991) have shown similar findings of decreased waveform pulsatility after shunting. Although an expected reduction in ICP after shunting was not confirmed by direct measurement of ICP, the significantly decreased RI, increased MFV and EDV postoperatively suggests that successful CSF diversion through shunting reduces ICP and improves cerebral perfusion as a result of reduced impedance to cerebral blood flow.

There was also little immediate change in ventricular size seen in the young infants after shunting as after ventricular CSF taps. These observations were similar to those reported by Horikawa (1991) who found a significant fall in waveform pulsatility after shunting while there was little change in ventricular size. This again adds further support to the view that in these patients the RI reflects the change in cerebrovascular resistance due to a decrease in ICP as a result of the CSF diversion rather than the degree of ventricular dilatation.

The case histories illustrate the use of serial monitoring of RI and MFV in hydrocephalic patients to monitor their progress after surgical procedures such as ventricular shunting or cyst drainage. Shunt infection or blockage prevents optimal shunt function and consequently cerebral perfusion may remain compromised as illustrated by cases 1 and 2. In the immediate period after ventriculo-peritoneal shunting changes in ventricular size or head circumference measurements are often not marked and thus not a reliable guide as to whether the newly inserted shunt is functioning effectively. Case no. 3 illustrates how serial RIs can be helpful as an additional assessment to ICP measurement in considering whether further surgery such as shunting would be required. It was particularly helpful as a non-invasive assessment after shunting because the lateral ventricles remained significantly dilated in this patient and thus the ventricular size was not a helpful guide at all to the efficacy of shunt function and the state of cerebrohaemodynamic balance.

This study illustrates the usefulness of TCD as a non-invasive method of assessing cerebrohaemodynamic changes after shunting as measurement of ICP through invasive needle puncture of the reservoir would risk the introduction of infection into newly inserted shunts.

5.6.3 CBFV in patients with functioning shunts

Hydrocephalic patients with shunts in-situ who present with a diversity of clinical symptoms can often be a diagnostic difficulty as these symptoms may or may not be related to shunt blockage or malfunction. Symptoms such as irritability, headaches and vomiting due to intercurrent illnesses eg. viral infections, often mimic those due to shunt blockage and it is usually not possible from clinical evaluation alone to be certain of the cause, especially as clinical signs such as papilloedema may either be absent or only apparent in the late stages (Kirkpatrick et al 1989). In particular chronic shunt malfunction is difficult to diagnose as the clinical signs and symptoms are often subtle and nonspecific.

These results suggest firstly that patients with hydrocephalus whose shunts are functioning well and thus in a 'compensated' condition with no raised ICP have no significant impairment of cerebral blood flow as CBFV values from these patients do not show any significant difference from normal healthy children. Secondly, as consistently similar RI values are found immediately after successful shunting and in patients known to have functional shunts, they illustrate the use of RI values as a reliable method of evaluating shunt function, as suggested by Chadduck et al (1991). Indeed the RI values in both groups of patients were very comparable to the RI values reported by Chadduck et al in their patient groups.

In the twelve patients who presented with clinical symptoms, their normal RI values indicated that their symptoms were not due to poor shunt function and this was subsequently confirmed by CT scans or direct ICP measurement. As a group the RI and MFV values in patients who presented with symptoms were not significantly different from those who had TCD examinations performed when they were seen at routine outpatient clinics and who were clinically asymptomatic. Overall the data suggests that RI values > 0.65 in patients more than 1 year of age is

highly likely to indicate poor shunt function but it is more difficult to be certain in infants where normal RI values are steadily decreasing over the first year of life and there are not well established reliable ranges from normal controls over this period.

TCD ultrasonography can thus be clinically very useful as an initial screening investigation when faced with a patient with symptoms which could be attributed to shunt malfunction especially when other investigations such as CT scanning are not immediately available. In our practice it has been particularly helpful in cases when a separate CSF reservoir is not present or no longer accessible for direct ICP measurement.

5. 6. 4 CBFV in patients with non-progressive ventricular dilatation.

CBFV data, in particular the RI values in suggested there was no marked cerebrohaemodynamic compromise in these patients despite the ventricular dilatation. Stable ventriculomegaly is associated with normal pulsatility (Deeg et al 1988, Norelle et al 1989, Huang & Chio 1991) presumably because an equilibrium is established with normal ICP and unimpaired cerebral perfusion. In some cases the ventriculomegaly is due to atrophic changes and raised ICP does not occur. In these cases shunting procedures would not confer any additional clinical benefit and would not be indicated (Huang & Chio 1991). The RI values from the study infants with non-progressive ventricular dilatation are similar to the RI values in three patients reported by Chadduck & Seibert (1989) who also did not require shunting. RI values >0.8 in young infants have been suggested in three separate studies (Horikawa 1991, Nishimaki, Chadduck & Seibert 1989) to indicate a requirement for shunting. The general agreement from these different studies again supports the RI to be a reliable index for assessment of hydrocephalic children.

It is important to recognise that a single measurement of RI has limited value in predicting if intervention may or may not be required. It is more helpful to serially monitor the RI in following the clinical course of individual patients during the period of assessment as shown in the case illustration (patient FR) previously. The RI value, if initially elevated, should be expected to gradually decrease to normal values if there is

'compensation' or 'arrest' of the hydrocephalic process. Conversely, if a patient who initially had RI values which were normal or only mildly elevated subsequently becomes symptomatic with accompanying abnormally high RI values, this may suggest a 'decompensated' state.

5.6.5 Volume-flow velocity response during sequential CSF drainage

Sequential RI measurements during CSF drainage from 53 taps in 18 patients were shown to fit a pattern of exponential decay. This suggests a possible model for directly predicting cerebrohaemodynamic change in response to CSF volume challenge in a similar manner to prediction of intracranial compliance from ICP changes. Change in CPP is usually assumed from the calculation $CPP = MAP - ICP$ whenever ICP is altered. However, the calculated CPP change may not accurately reflect true perfusion changes if there are compensatory peripheral resistance alterations to accommodate a fall in CPP. Decrease in RI during hypercapnia-induced increase in CBF suggests that the RI may be a reliable index of distal cerebrovascular resistance (Archer et al 1986). These results suggest that there may also be an exponential cerebrohaemo-dynamic response to CSF volume changes. This could allow prediction of a 'volume-buffering' reserve before significant cerebrohaemodynamic compromise occurs with increased resistance to flow.

The three patients who have remained unshunted with stable i.e. arrested hydrocephalus have been clinically stable with no progressive neurological deficit, thus suggesting that even with persistently dilated ventricles their cerebral perfusion has not been significantly compromised. They had larger 'half-volumes' from their VFR studies which may suggest a larger volume-buffering reserve. Patient VH showed a larger 'half-volume' with accompanying clinical improvement which may suggest that an increasing 'half-volume' could be an indicator of increasing 'volume-buffering' reserve as the hydrocephalic process reaches a state of 'arrest'.

Single measurements of RI, especially without accompanying ICP data in neonatal or young infants, as previously discussed, can be unreliable as some with an elevated RI may not necessarily have significantly increased ICP (Hill & Volpe 1981) and there is overall a poor correlation when

comparing different patients in this age group. Thus some young infants may have considerably increased cerebrovascular resistance with reduced perfusion due to the hydrocephalus even without markedly raised ICP levels. Prediction of progression or arrest in the hydrocephalus can be very difficult with such individual variability in the range of ICP or RI values seen but is nevertheless important if we aim to avoid unnecessarily shunting those who may 'arrest' spontaneously while needing to prevent secondary ischaemic damage in those who show further progression and require shunting. These studies of serial change in RI with volume drainage suggest that estimation of 'half-volumes' as an indicator of buffering reserve may potentially be useful for prediction in individual cases. However, the number of patients studied so far, in particular those in the group which showed spontaneous arrest, have been very small and thus these results are not conclusive. Nevertheless these results suggest that further research with a prospective study involving more patients is required and this method of assessing sequential CBFV change could indeed be a very promising aid towards more accurate prediction.

5. 6. 6 Simultaneous CBFV and ICP changes during sleep.

There is considerable scepticism regarding the reliability of Doppler flow velocities to reflect true volume flow changes. Doppler flow velocities cannot provide absolute measurements of CBF and although normal ranges of MFV are available and there have been a large number of studies validating the reliability of MFV values as a guide to CBF values, interpatient comparisons of doppler flow are still best avoided as there can be wide variations of individual cerebral arterial cross-sectional diameter. However, interpretation of CBFV changes can, with due caution, in strictly regulated situations, provide a reliable non-invasive measure of cerebrohaemodynamic *trends* in individual patients over a short period of time. In such situations a progressive decrease in MFV and increase in RI as ICP increases suggests a decreasing mean flow with increasing distal resistance. Conversely an increased MFV response suggests that mean flow may be increased despite a rise in ICP.

In this study change in the MFV is likely to provide a reliable index of mean volume flow changes over the duration of each individual

recording as the Doppler measurements were performed from a constant position and at a constant depth throughout once the optimal position was selected at the beginning of each study. A potential source of error for hand-held intermittent Doppler recordings may be inexact repetition of the angle of insonation. Changes in absolute velocity indices such as the MFV, PSV and EDV will be more significantly affected whilst the RI, as a ratio, minimises this potential error. In practical terms I endeavoured to maintain a constant angle through rigorously selecting only optimal clear signals from the same position at frequent intervals or continuously during changing ICP states whilst rejecting signals distorted by movement. During normal sleep in children, even with the use of a headband to allow fixation of the transcranial probe, frequent adjustment for optimal signals and exclusion of poor quality or distorted waveforms by an experienced operator on-site would still be required as normal spontaneous head movements can easily cause dislodgement of the probe. Error in the measurement of CBFV in this study due to a varying angle of insonation while still possible is not likely to be important.

It has been assumed to be unlikely that there would be any significant change in MCA diameter to affect CBFV measurements over the duration of each of these studies as firstly there was no evidence of cerebral vascular disease in these young patients and secondly, autoregulatory response occurs mainly through alteration of calibre in distal resistance vessels (Kato and Auer 1989) rather than in a major artery such as the MCA.

A possible explanation for the observed increased MFV response to ICP rise could have been due to progressive narrowing of the MCA rather than a true increase in mean volume flow. As none of the studies with an increased MFV response had MFV values over 100 cm/sec, it is not likely that vasospasm of the MCA would have been responsible for the observed increase in MFV. While it is assumed to be unlikely that significant diameter changes would occur in a major vessel such as the MCA in these study patients in response to ICP elevations in sleep, it is necessary to note that recent experimental studies have raised the possibility of some alteration in vessel calibre in response to local haemodynamic forces, haematocrit and $p\text{CO}_2$ (Brant et al 1987, Melkumyants et al 1989, Melkumyants et al 1990). It was thought in one study that up to $\frac{1}{3}$ total

cerebrovascular resistance could be attributed to cerebral arteries of more than 150 micrometer diameter (Faraci et al 1987). In other studies of both humans and animals, during reductions in systemic blood pressure, the change in calibre of large cerebral arteries was found, however, to be relatively small, generally <5% (Heistad et al 1978, Kontos et al 1978, Harder 1984, Radu & duBoulay 1976). With continuous monitoring, although the errors introduced by assumption of unchanging calibre may be significant, they are perhaps acceptable. Velocity changes at the point of insonation in the MCA should reasonably reflect mean flow changes effected by changes in the distal resistance vessels if the above assumptions are correct.

It has been established that cerebral blood flow increases during rapid eye movement sleep (Reivich et al 1968, Sawayawa and Ingvar 1989), probably mediated by distal arteriolar vasodilatation. Thus in patients with underlying defective CSF absorptive mechanisms, the resulting increase in intracranial blood volume is inadequately buffered producing a greater rise in ICP. Sustained plateau (A) waves are thought to occur as a result of autoregulatory responses in those with decreased intracranial compliance, elevated ICP and an unstable CPP (Rosner and Becker 1984). In this study, assessment of the periods of elevated ICP, as a percentage of the total ICP recording did not clearly separate out those who showed a *decreased MFV* response from those with an *increased MFV* response to rise in ICP. The mean duration of unstable ICP periods was 31.6% for the decreased MFV response group and 26.4% for the increased MFV response group. For appropriate management the important question is the clinical significance of these episodic ICP increases for each individual patient so that we can avoid unnecessary surgical procedures in those who can haemodynamically compensate adequately whilst also seeking to prevent secondary ischaemic insult in those who are at risk.

Minns (1991) found that patients with slit ventricles and high ICP spent a significantly greater period of their sleep with compromised CPP levels compared to other groups of hydrocephalic patients. Prolonged mean transit time for cerebral isotope clearance suggesting reduced circulatory reserve was significantly related to reduced CPP as a result of raised ICP (Minns and Merrick 1989). Gibbs et al (1984), using PET scans, have

reported that prediction of residual perfusion reserve from the ratio of cerebral blood flow to blood volume was a reliable way of identifying patients with carotid artery occlusion who were most haemodynamically compromised. In this study the Type I (decreased MFV) response to rise in ICP with rise in RI suggests that raised ICP which may be initiated by a small increase in cerebral blood volume can lead to a substantial rise in cerebrovascular resistance and result in diminished cerebral blood flow reflected by the decreased MFV. In experimental animals Barzo et al (1991) showed that the decreased cerebrovascular resistance that accompanied the decreased cerebral blood flow and CBFV was autoregulatory down to a perfusion pressure of 40 mmHg. Below this level (i.e. with loss of autoregulation) they found an increase in cerebrovascular resistance which they suggested was due to the intracranial hypertension blocking cerebral venous outflow. As a result of the increasing resistance, cerebral blood flow and CBFV progressively diminished despite maximal vessel dilatation.

During plateau (A) and B intracranial pressure waves the marked decreased MFV response suggests that circulatory reserve may be critical during these episodes. In an experimental cat model Kato and Auer (1989) showed that when ICP was increased from 13 to 45 mmHg by ventricular infusion of mock CSF, significant pial arterial dilatation of 40% occurred. However, with further rise of ICP no further arterial dilatation occurred. Thus maximum cerebrovascular compensation has already occurred and any subsequent further increase in ICP is likely to result in reduced perfusion. The patients with a Type I response who showed decreased MFV with decreasing CPP demonstrated this loss of haemodynamic compensation with progressive decrease of perfusion pressure and were thus at greater risk of ischaemic insult from decreased blood flow, especially those with reduced intracranial compliance such as the three patients with slit-ventricles. This Type I response was abolished in patient no. 3 after an intracranial volume enhancing procedure (by skull morcellation) which should improve intracranial compliance and hence also perfusion reserve.

In the studies with a Type II (increased MFV) response to rise in ICP, the data suggests that appropriate cerebrovascular response to moderately

increased ICP during sleep may occur. This is probably mediated through distal pial arterial dilatation and increased cerebral blood flow to maintain an adequate perfusion. This is more likely in patients who have adequate circulatory reserve and hence a Type II response to rise in ICP may provide a means of identifying patients who are able to compensate haemodynamically to episodic pressure elevations with little risk of ischaemic insult. During these studies the MFV increased despite a decreasing CPP due to increase in ICP. This reinforces that evaluation of CPP change alone may not reliably predict those whose cerebral perfusion remains adequate despite a rise in ICP.

The RI increased with increasing ICP in all but one study. Change in distal cerebrovascular resistance will also be influenced by other factors such as existing transmural pressure, vascular compliance and cerebral blood volume in the arterial and venous compartments. In three studies with an increased MFV response, RI increased correspondingly as ICP increased; hence although distal impedance to flow may be increasing due to increased ICP, the net result is still that perfusion is maintained by increased mean volume flow while cerebral blood volume would probably not have been markedly increased. In one patient (no.7) increased MFV was associated with a decrease in distal resistance during rise in ICP, therefore there could be further dilatation of resistance vessels, reducing the distal impedance. With a corresponding increase in mean volume flow there may have been, in this patient, a net increase in cerebral blood volume. However, without being able to quantitate absolute CBF nor its ratio to blood volume it would not be possible from the Doppler technique alone to reliably predict the separate effects on cerebrovascular resistance and net perfusion.

Studies in adult patients in coma (Hassler et al 1988, Klingelhofer et al 1988) have reported a consistent increase in pulsatility of CBFV waveforms with decreased MFV and increased RI during major increase in ICP i.e. equivalent to the Type I (decreased MFV) response in those patients with limited circulatory reserve. These results suggest, however, that in children with compensated hydrocephalus, appropriate haemodynamic response (i.e. *increased MFV* response) to maintain adequate perfusion may occur during episodic moderate increase of ICP in

sleep. Given the limitations of current widely available commercial TCD systems which are unable to accurately measure cerebral vessel diameter, nevertheless simultaneous monitoring of CBFV and ICP changes in hydrocephalic patients can still provide additional information on cerebrohaemodynamic *trends* which may help to identify those who are at greater risk of ischaemic insult (those with *decreased MFV* response) from episodic increases in ICP. This could help in more appropriate selection of patients who will benefit from surgical procedures especially when there is clinical uncertainty in patients with nonspecific symptoms.

5.6.7 Conclusion

These six studies of TCD monitoring in hydrocephalic children suggests that it can be of considerable value in the clinical assessment of childhood hydrocephalus. In particular the RI appears to be a highly reliable index in the assessment of hydrocephalic patients as it shows a reliable correlation with ICP in individual neonates or overall in older children. It has been shown in these studies, in agreement with other reports in the literature, to be consistently raised in patients prior to shunting or taps or in those with malfunctioning shunts i.e. when ICP or cerebrovascular impedance would be expected to be high. The association of decreased RI along with increased EDV and MFV after effective CSF drainage, through taps or shunts, supports it to be a reliable index of distal resistance.

The most reliable use of the RI, however, as discussed, is in serial monitoring of each individual patient, rather than in single measurements for inter-subject comparisons. In the early assessment period this is particularly useful for evaluating if the hydrocephalus appears to be progressive or causing significant cerebrohaemodynamic compromise. In hydrocephalic children who present with symptoms, TCD examinations showing a raised RI value compared to RI values when clinically well, especially when it is associated with decreased EDV and MFV values highly suggests that these symptoms are likely to be associated with raised ICP. Conversely a normal RI would suggest that the symptoms are more likely to be due to alternative causes such as intercurrent infections. Thus for each individual, the RI serves as a reliable index for initial evaluation, and further monitoring of shunt function if shunted or careful assessment if remaining unshunted.

Other CBFV values, i.e. the MFV, EDV and PSV appear to be less consistent in each individual case for the purpose of serial measurements or monitoring and unreliable for intersubject comparisons. This may be due in part to a variable angle of insonation on each occasion and in each individual as cerebral blood vessels may be significantly distorted in their course by the ventricular dilatation. These values are more greatly affected by a varying angle of insonation whereas the RI, being a ratio, would theoretically be independent of this effect. However, at very low velocities, the EDV may be more markedly affected than the PSV and this would influence the RI value too. Intersubject comparisons of absolute velocity values are difficult to interpret as in addition the cross-sectional arterial vessel diameter can vary widely and CBFV values cannot be readily compared as mean flow values between individuals. However, as shown in the sleep study, under strict measuring conditions, MFV values may indicate *trend* changes in flow over a defined period of time for individual patients.

The VFR studies suggest a possible method of evaluating cerebrohaemodynamic response to predict volume-buffering reserve in hydrocephalic children. The numbers of children studied were small but the exponential relationship shown between RI and volume of CSF drained in the majority of the taps does suggest that there is a critical point when cerebrovascular resistance is altered significantly in a similar manner to ICP dynamics. Serial VFR studies could help in more accurate prediction of progression or arrest of hydrocephalus for each individual and thus guide appropriate selection of those who will benefit from shunting whilst avoiding shunts and their early and longterm complications in those who would spontaneously arrest. More studies, of a prospective nature in those who show spontaneous 'arrest' will be required.

The sleep studies with simultaneous ICP and Doppler monitoring, also of a small number of patients, show the value of dynamic and more prolonged monitoring. It has long been recognised that ICP dynamics in hydrocephalic patients can be complex and can vary considerably in different conditions such as during sleep where alterations of cerebral blood flow in different stages of sleep can cause periods of marked ICP

elevation not usually seen in the awake state. These patients are often difficult to assess as their symptoms are often of a chronic, nonspecific nature and the cerebrohaemodynamic consequence of these periods of ICP elevation are difficult to evaluate. Combined ICP and Doppler monitoring in these situations appears to be helpful in assessing if there is adequate cerebrohaemodynamic reserve to compensate for these periods of ICP elevation (the increased MFV response) or whether there is inadequate cerebrohaemodynamic reserve (decreased MFV response) with thus greater risk of compromised perfusion during these periods. This would help in better selection of those who will derive benefit from any further surgical procedures.

In conclusion, TCD ultrasonography offers a clinically useful and reliable method for non-invasive assessment and monitoring of children with hydrocephalus. More useful information can also be derived by utilising it in serial and dynamic studies as shown depending on the clinical circumstances.

TCD MONITORING IN MENINGITIS

6.1 Introduction

Bacterial meningitis is one of the most serious diseases in early childhood with a reported overall mortality rate of 8.6% in the first year of life (de Louvois et al 1991). However, although mortality rates have improved there is still a considerable long-term morbidity ranging from 10 - 15% (Pomeroy et al 1990). Impaired cerebral perfusion resulting from a variety of factors plays a significant role in the pathogenesis of cerebral injury in meningitis (Tunkel et al 1990, Saez-Llorens et al 1990). A minimum CPP of 30 mmHg was found to be a significant pointer for survival in children who were comatose from severe central nervous system infection (Goiten et al 1983, Rebaud et al 1988). Minns et al (1989) have reported raised CSF pressure to be a frequent accompaniment of pyogenic meningitis. Raised ICP is likely to be an early feature in the pathophysiology of pyogenic meningitis (Tunkel et al 1990, Rebaud et al 1988) and contributes to reduced cerebral perfusion.

The pathogenesis of cerebral injury in bacterial meningitis is a complex interaction of a number of inflammatory processes which leads to brain oedema, raised intracranial pressure and diminished cerebral perfusion. After meningeal invasion and bacterial replication within the subarachnoid space the release of bacterial products in the CSF stimulates host defence mechanisms which leads to the production of inflammatory mediators such as tumour necrosis factor and interleukin-1 from leucocyte, macrophage and endothelial cells. These inflammatory processes lead to injury to the vascular endothelium resulting in increased blood-brain barrier permeability and activation of the coagulation cascade. Clinical (Rebaud et al 1988) and experimental (Pfister et al 1990) studies suggests that cerebral oedema may occur early and may be vasogenic, cytotoxic or interstitial in origin. Vasogenic cerebral oedema occurs as a result of the increased blood-brain barrier permeability. Cytotoxic oedema (brain cell swelling) occurs as a consequence of the release of toxic substances from the increased number of leucocytes. Interstitial oedema

also occurs as CSF outflow resistance increases during meningitis (Scheld et al 1980) and may lead to the development of hydrocephalus.

A significant rise in ICP due to brain oedema may result in diminished CBF if cerebral perfusion pressure is markedly reduced. In experimental models the early rise in ICP may, however, be associated with increased CBF within the first six hours (Pfister et al 1990, Tureen 1989) although this hyperemic phase is followed by progressive decline in CBF by 16 to 20 hours (Tureen et al 1989). This reduction at 20 hours was highly associated with progressive CSF lactic acidosis. Tauber (1989) reported a progressive reduction of blood flow particularly in the subcortical white matter with increasing severity of disease in animals infected with different pneumococcal strains. Ashwal et al (1990) also found a greater reduction of blood flow in white matter compared to grey matter in 5 of 20 seriously ill children who had significantly reduced total CBF. Total blood flow was uniformly absent in two infants brain dead within the first 24 hours. Thus irreversible ischaemic brain damage may occur as a consequence of the diminished CBF. Loss of cerebrovascular autoregulation in meningitis (Tureen et al 1990) may also be a contributory mechanism. When CBF is pressure-passive perfusion can become markedly compromised with systemic hypotension while hypertension may be associated with increased flow, increased cerebral blood volume and further elevation in ICP.

The inflammatory effects on the cerebral micro- and macro-vasculature produces a vasculitis which results in luminal narrowing and thrombus formation; causing arteritis, vasospasm and stenosis, cortical thrombophlebitis leading to thrombosis, with further risk of secondary cerebral infarction or ischaemia (Raimondi & Di Rocco 1979). Cerebral vasospasm may be produced by the surrounding purulent material, this may be followed by local vasodilatation in association with myonecrosis and the final phase of organic stenosis in the repair process due to organisation of subendothelial oedema with resultant intimal thickening (Yamashima et al 1985). Involvement of large cerebral arteries is associated with serious neurologic complications and a poor outcome (Igarashi et al 1984).

Ventriculomegaly and subdural collections are well recognised complications (Snyder 1984). However, cerebral infarction and oedema shown by CT scans were predictive of a poor outcome while enlarged ventricular and subarachnoid spaces and subdural effusions were of no predictive value (Pike et al 1990). Thus the effect of impaired cerebral perfusion has greater impact on outcome while complications such as enlarged ventricular spaces or effusions need not have a deleterious effect if perfusion is not compromised. No single modality of monitoring can provide all the required information in understanding the complex balance of intracranial haemodynamic and hydrodynamic processes occurring in ill children with meningitis. However, monitoring cerebrohaemodynamic trends may be important for early detection of cerebral perfusion compromise with the aim of preventing further cerebral insult.

Xenon-computed CT scans have been reported to provide information on regional perfusion states as well as absolute levels of perfusion in meningitis (Ashwal et al 1990) but cannot be frequently repeated particularly in young children because of the risks of radiation exposure. A recent report (Giller et al 1990) has suggested that CBF itself may be rapidly changing during the process of xenon CT scanning due to xenon-induced vasodilatation.

TCD ultrasound provides a non-invasive and practical means for bedside monitoring in these ill children. It has been applied in bedside monitoring of cerebrohaemodynamic trends in neurointensive care management (Lundar et al 1990). There have, however, only been two published reports on CBFV changes in childhood meningitis (McMenamin & Volpe 1984, Bode & Harders 1989). McMenamin and Volpe reported a depressed mean velocity associated with raised ICP in 4 older infants (mean age 5.75 months) during the initial phase of the illness. In contrast decreased mean velocity and raised ICP was not present in their 4 newborn patients. Bode and Harders (1989), however, reported a marked (up to 5 fold) and persistently increased MFV from the MCA in 3 of their 14 cases with meningitis which was attributed to significant vessel narrowing causing secondary ischaemic damage as these patients had a poor outcome. The moderately increased flow velocities

in their 11 cases with a favourable outcome was ascribed to increased cerebral blood flow.

The results from using TCD ultrasound to monitor cerebrohaemodynamic changes in 17 children who were admitted with pyogenic meningitis to the Royal Hospital for Sick Children, Edinburgh are described.

6.2 Patients and Methods

Seventeen patients (9 males, 8 females) who were admitted with a diagnosis of pyogenic meningitis were monitored during the course of their admission by TCD. Their clinical details are summarised in Table 6 (i). Their age range was from 8 days to 6 years; 4 patients were less than 3 months old (Group I) and 13 patients were between 6 months - 6 years old (Group II). The patients were allocated to two groups as the normal range of CBFV data is age-dependent, and also to allow comparison with previously published data from neonatal and older infants with meningitis as reported by McMenamin and Volpe (1984). Initial TCD examination was performed within the first two days after admission and then repeated at intervals during their admission, more frequently during the early days. Three patients were transferred from other hospitals after failing to improve satisfactorily. Three patients required ventilatory and intensive care support on admission. In 4 patients CBFV recordings with simultaneous ICP and CPP measurements before and after mannitol infusions were obtained. Cerebral imaging by transfontanelle ultrasonography was performed in 10 infants and CT scans in 3 children with clinical signs of raised ICP or with persistent pyrexia and irritability.

The organisms isolated from the CSF were Group B haemolytic streptococci (2), *Eschericia coli* (1), *Neisseria meningitidis* (5), *Haemophilus influenzae* type b (6), *Streptococcus pneumoniae* (1) and *Salmonella enteritidis* (1). In one patient (no. 12) who had received antibiotics prior to admission and before CSF was obtained (lumbar puncture deferred till the second day), no specific bacterial or viral agent was isolated and countercurrent immunoelectrophoresis antigen screening was also negative. His CSF leucocyte count was markedly

elevated (4500/cu mm, 84% neutrophils) and he showed a rapid clinical response to antibiotic therapy thus suggesting a bacterial aetiology. There was only one fatal outcome (case no. 1: a 2 week old neonate with Group B haemolytic streptococcal infection) in this study.

TCD examinations were carried out at the bedside when patients were asleep or quiet. The CBFV data was often most easily obtained in the early acutely ill stages as the patients were usually drowsy and lethargic at this stage. Values of the MFV, PSV, EDV and the RI were obtained. These patients were mostly breathing spontaneously in room air. In those who were ventilated, pCO₂ was maintained within the normal range (3.5 - 5.5 kPa). None of these patients had a patent ductus or other congenital heart lesion.

The paired t-test was used to compare changes between the initial and final (obtained prior to discharge) CBFV values in the 16 survivors. Correlation analyses between RI and MFV with ICP, CPP and MAP values were performed in 5 patients where these measurements were available.

6.3 Results

6.3.1 Resistance Index (RI)

Table 6 (ii) shows the initial and final CBFV values from the 16 survivors. In ten of the patients there was an elevated RI ($> \text{mean} + 2 \text{ sd}$) at the initial TCD examination. Serial measurements of RI decreased with resolution of infection and clinical improvement (see Figure 6.1 - Group I, Figure 6.2 - Group II) and final RI values were within normal range at discharge in all survivors. There was a highly significant decrease in RI ($p < 0.001$) from paired t-test analysis of initial and final RI values in the 16 survivors. In the Group I survivors, mean RI decreased from 0.81 to 0.72, and in Group II survivors mean (sd) RI decreased from 0.67 (.06) to 0.545 (.04). The decrease in RI was mainly due to a significant increase in EDV ($p = 0.001$) rather than to change in PSV (not statistically significant).

Figure 6.1 shows the serial RI values with recovery in three Group I infants. Figure 6.2 shows the serial mean RI values from ten Group II patients who responded fully to intravenous antibiotic therapy only

without significant further complications. Serial RI values from three Group II patients were not included in the calculation of these mean values as these three patients received additional intrathecal antibiotics when there was clinical and laboratory evidence (persistently raised CSF neutrophil count or positive bacterial growth) of inadequate sterilisation of the CSF. Also shown in Figure 6.2, in contrast to the ten patients who had a good response to intravenous antibiotics, are more persistently elevated serial RI values from one of the patients who required additional intrathecal antibiotics. This patient with pneumococcal meningitis developed communicating hydrocephalus and bilateral subdural effusions and required intrathecal penicillin in addition to sterilise the CSF. Overall, there was no difference in the pattern of RI change between Group I and II patients.

Table 6 (i) Clinical details of patients with pyogenic meningitis

Case No.	Age	Sex	CSF organism	Diagnostic CSF			Radiological findings	Outcome at discharge
				leucocytes /mm ³	protein (g/L)	glucose (mmol/L)		
1	2 wks	F	Gp B strep	515	8.9	nil	US: oedema, focal echogenicity	Died
2	8 days	M	E coli	10,400	4.18	2.3	US: normal	normal
3	13 days	F	Gp B strep	565	blood	stained	US: normal	normal
4	11 wks	F	H. influenzae	1400	0.97	<0.5	US: bilateral subdural effusions	normal
5	9 mths	M	N. meningitidis	7100	1.38	<0.3	-	normal
6	8 mths	M	H. influenzae	4930	0.92	<0.5	US: bilateral subdural effusions	normal
7	8 mths	F	H. influenzae	1930	0.54	3.5	-	normal
8	11 mths	M	N. meningitidis	20,800	2.92	<0.5	-	normal
9	26 mths	M	H. influenzae	650	1.28	0.9	-	normal
10	8 mths	F	N. meningitidis	6650	1.21	1.6	US: normal	normal
11	23 mths	F	N. meningitidis	10,000	-	-	-	normal
12	6 mths	M	-	4500	2.3	2.9	US: normal	normal
13	19 mths	M	H. influenzae	1605	4.06	<0.5	CT, MRI scans: normal	mild ataxia
14	7 mths	M	S. pneumoniae	1780	33.0	0.5	US & CT scans: bilat subdural effusions, (Rt: increased density); communicating hydrocephalus	left focal seizures, mild left sided weakness
15	8 mths	F	H. influenzae	2350	0.75	4.0	US: widened subdural spaces, echogenic cortical sulci	normal
16	6 mths	M	N. meningitidis	140	0.42	3.2	US: bilat subdural effusions, slight ventricular dilatation.	normal
17	6 yrs	F	Salmonella enteritidis	372	2.66	<0.5	CT scan : mild prominent ventricles, no focal lesion	normal

Table 6 (ii) Initial and Final CBFV values in 16 survivors with meningitis

Case No.	Age	Initial RI	Final RI	Initial MFV cm/sec	Final MFV	Initial PSV cm/sec	Final PSV	Initial EDV cm/sec	Final EDV
2	8 days	0.80	0.71	41.5	43.8	81.0	78.0	16.0	22.0
3	13 days	0.86	0.75	29.3	37.9	67.8	37.9	9.5	16.0
4	11 wks	0.76	0.69	40.4	68.0	71.3	110.0	17.3	32.4
5	9 mths	0.59	0.49	71.7	82.0	109.0	113.0	46.0	57.0
6	8 mths	0.66	0.52	55.9	56.9	95.8	81.9	32.8	37.3
7	8 mths	0.72	0.61	49.6	70.6	88.5	108.2	25.1	42.6
8	11 mths	0.58	0.56	68.2	83.0	108.0	117.0	45.0	51.0
9	26 mths	0.67	0.54	65.3	89.8	122.0	129.0	40.4	57.3
10	8 mths	0.61	0.50	89.8	85.4	145.4	120.8	56.9	60.6
11	23 mths	0.75	0.53	40.9	73.2	80.1	105.5	19.1	48.1
12	6 mths	0.64	0.50	68.0	75.4	110.0	106.0	40.0	52.4
13	19 mths	0.68	0.60	69.2	57.4	124.0	92.3	40.0	35.0
14	7 mths	0.79	0.58	37.2	76.6	80.8	117.8	17.8	49.1
15	8 mths	0.69	0.59	67.3	71.0	120.1	112.3	37.9	45.4
16	6 mths	0.64	0.55	81.8	77.9	141.2	113.9	49.4	51.0
17	6 yrs	0.73	0.52	46.3	102.0	98.1	159.6	25.7	73.5
mean value (sd):		0.70 (.08)	0.58 (.08)	57.6 (17.5)	71.9 (16.5)	102.7 (23.8)	108.4 (21.4)	32.4 (14.0)	45.7 (14.6)
p value:		<0.001		<0.01		0.39 (ns)		0.001	

Figure 6.1 : serial RI values in Group I (<3 mths old) survivors

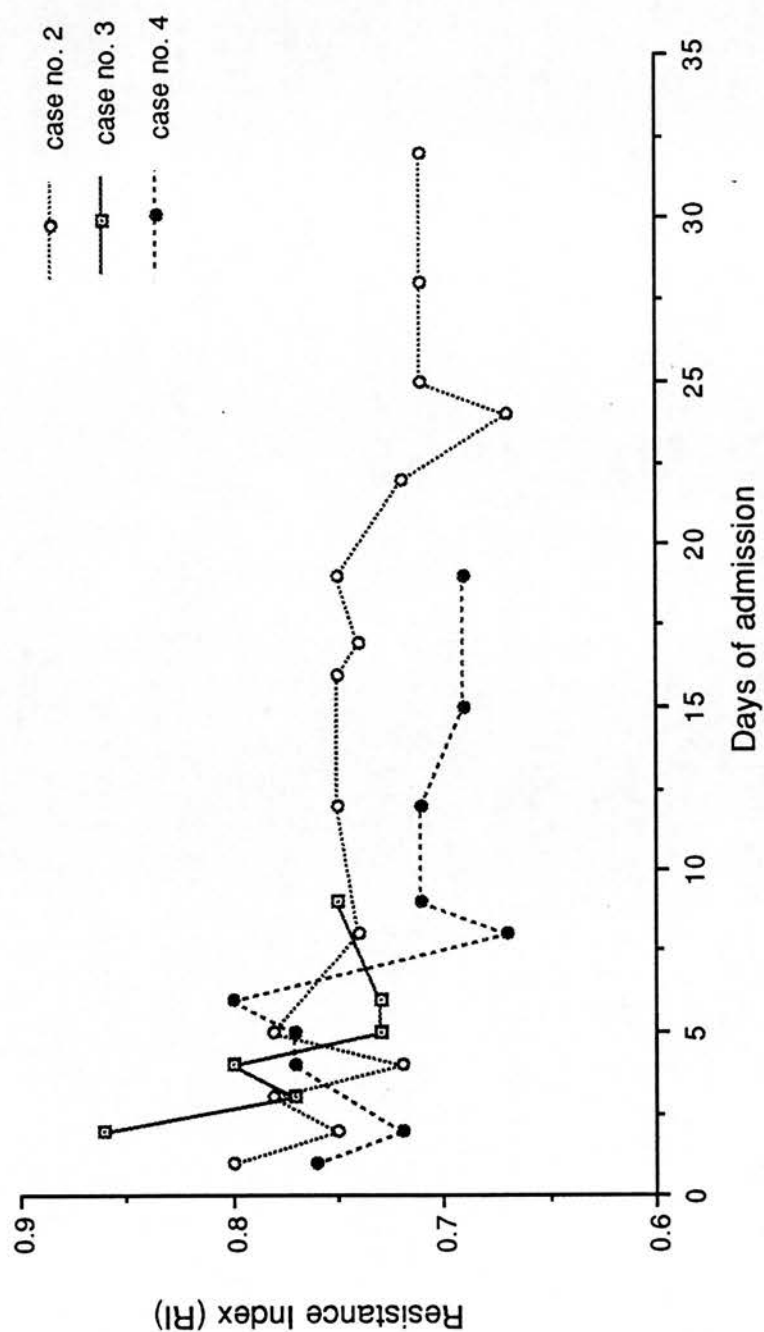
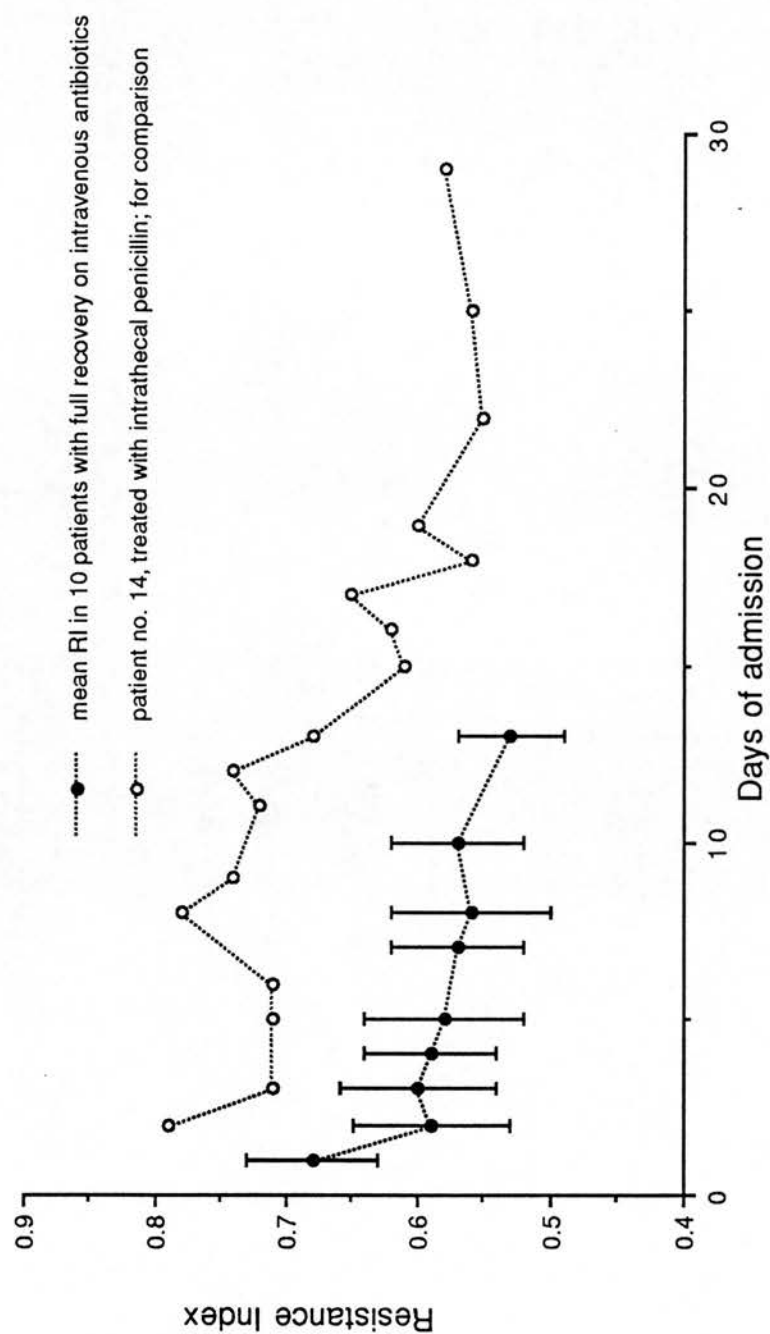


Figure 6.2 : serial RI values in Group II (> 3 mths old) patients with meningitis



6.3.2 Mean Flow Velocity

Three patients had an initial MFV less than normal range for age. Overall, final MFV in the 16 survivors was significantly increased compared to initial MFV ($p < 0.01$) on paired t-test analysis which may suggest increased mean CBF with recovery from infection compared to initial values at admission. Two patients in this study had MFV >120 cm/sec on one occasion each; patient no. 11 on day 3 (120.2 cm/sec) and patient no. 17 on day 2 (132.3 cm/sec). However, the elevated MFV values did not persist in both these patients and were within normal range on the next day. In individual patients serial MFV values on a day to day basis were more variable compared to a more consistent decreasing pattern for serial RI values.

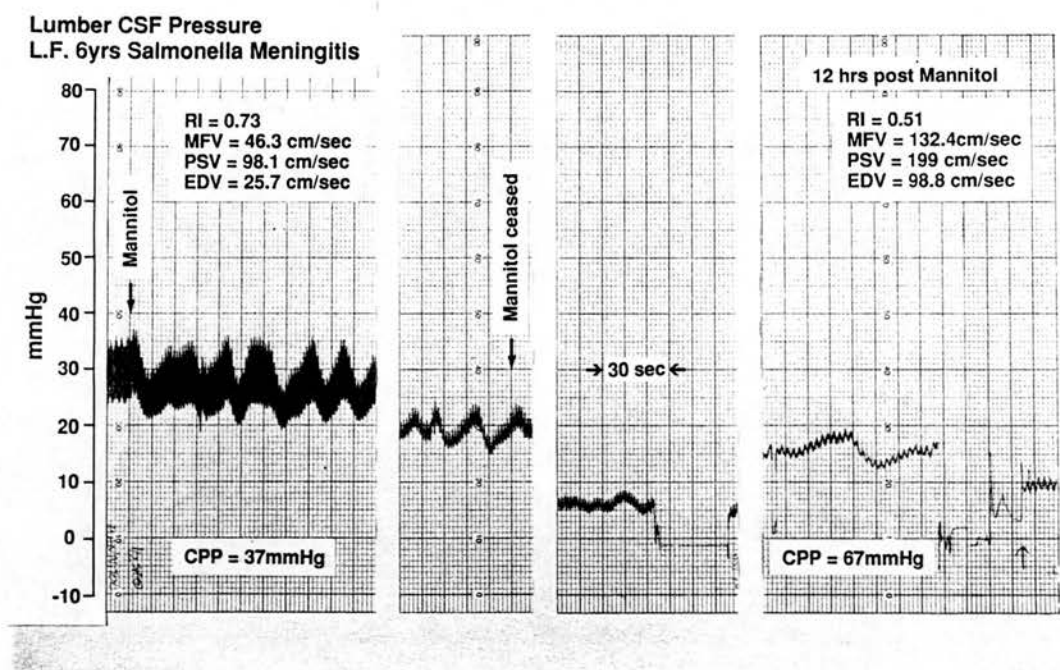
6.3.3 CBFV changes after mannitol

In 3 patients simultaneous TCD and ICP recordings were carried out on the day of admission before and after mannitol infusions. Table 6 (iii) shows the ICP, MAP, CPP and CBFV values before and after mannitol infusions. In these patients as CPP increased with decrease in ICP after the mannitol infusions there was accompanying improvement in CBFV values, with decrease in RI and increase in MFV. In patient no. 16 lumbar puncture was deferred until after the mannitol infusion when RI had decreased from 0.64 to 0.59, and MFV increased from 81.8 to 96.9 cm/sec.

Table 6 (iii) Changes in ICP, CPP and CBFV values before and after mannitol infusions in 4 patients

Case No.	Age	Pre/post mannitol	MAP (mmHg)	ICP (mmHg)	CPP (mmHg)	RI	MFV (cm/sec)	PSV (cm/sec)	EDV (cm/sec)
11	23 mths	Pre- mannitol	69	28	41	0.82	36.7	78.5	12.2
		Post-	68	10	58	0.67	59.0	106.0	34.4
15	8 mths	Pre-mannitol	72	19	53	0.69	68.1	120.1	37.1
		Post-	72	10	62	0.60	91.6	139.1	54.5
16	6 mths	Pre-mannitol	81	-	-	0.64	81.8	141.2	49.4
		Post-	62	17	45	0.59	96.9	156.0	61.7
17	6 yrs	Pre-mannitol	65	28	37	0.73	46.3	98.1	25.7
		12 hrs post	77	10	67	0.51	132.3	197	98.8

Figure 6.3: ICP recordings with corresponding CBFV and CPP values from patient no. 17 with salmonella meningitis at initial lumbar puncture and 12 hours later

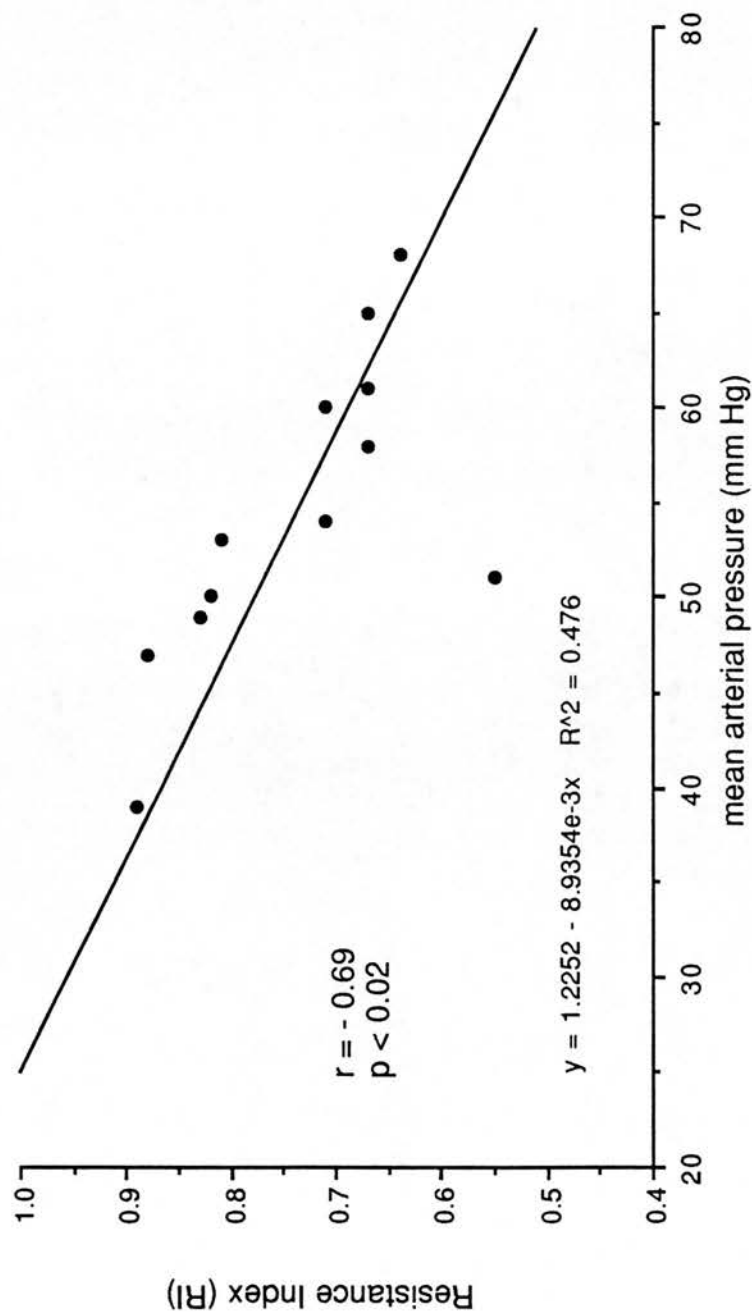


6.3.4 Pressure-passivity

A two week old girl (patient no. 1) with Group B haemolytic streptococcal meningitis and septicaemia required early ventilation and inotrope support in addition to systemic antibiotics, dexamethasone and anticonvulsants for increasing frequency of apnoeic episodes and a poor peripheral circulatory state. Cerebral ultrasound scan showed collapsed lateral and third ventricles with increased echogenic areas in both parietal regions suggesting the presence of cerebral oedema and focal areas of intracranial haemorrhage or infarcts. Through a subarachnoid catheter the initial ICP measured was 6 mmHg while MAP was 50 mmHg. However, she remained unstable with frequent bradycardic episodes while there were intermittent ICP elevations to 20 - 30 mmHg despite mannitol infusions. There was further deterioration over the next two days with a labile systemic blood pressure and frequent hypertensive and bradycardic episodes. On the third day of admission her EEG showed electrocerebral silence, pupils were unresponsive and she died the next day. TCD recordings showed that she had a pressure-passive CBFV response to changes in systemic blood pressure (Figure 6.4) with a significant linear correlation between RI and MAP ($r = -0.69$, $p < 0.02$), which may suggest loss of cerebrovascular autoregulation. Postmortem examination confirmed congested and swollen cerebral tissue, compressed ventricular system, thrombosed vessels over both temporal poles with intraparenchymal and subarachnoid haemorrhages.

In contrast the other 2 patients who also required intensive care support and treatment for intracranial hypertension did not show a pressure-passive CBFV response. This suggests that no loss of cerebrovascular autoregulation occurred during the acutely ill stage in these two survivors.

Figure 6.4 : RI / MAP correlation in a neonatal patient with Group B haemolytic strep. meningitis showing a pressure - passive CBFV response.

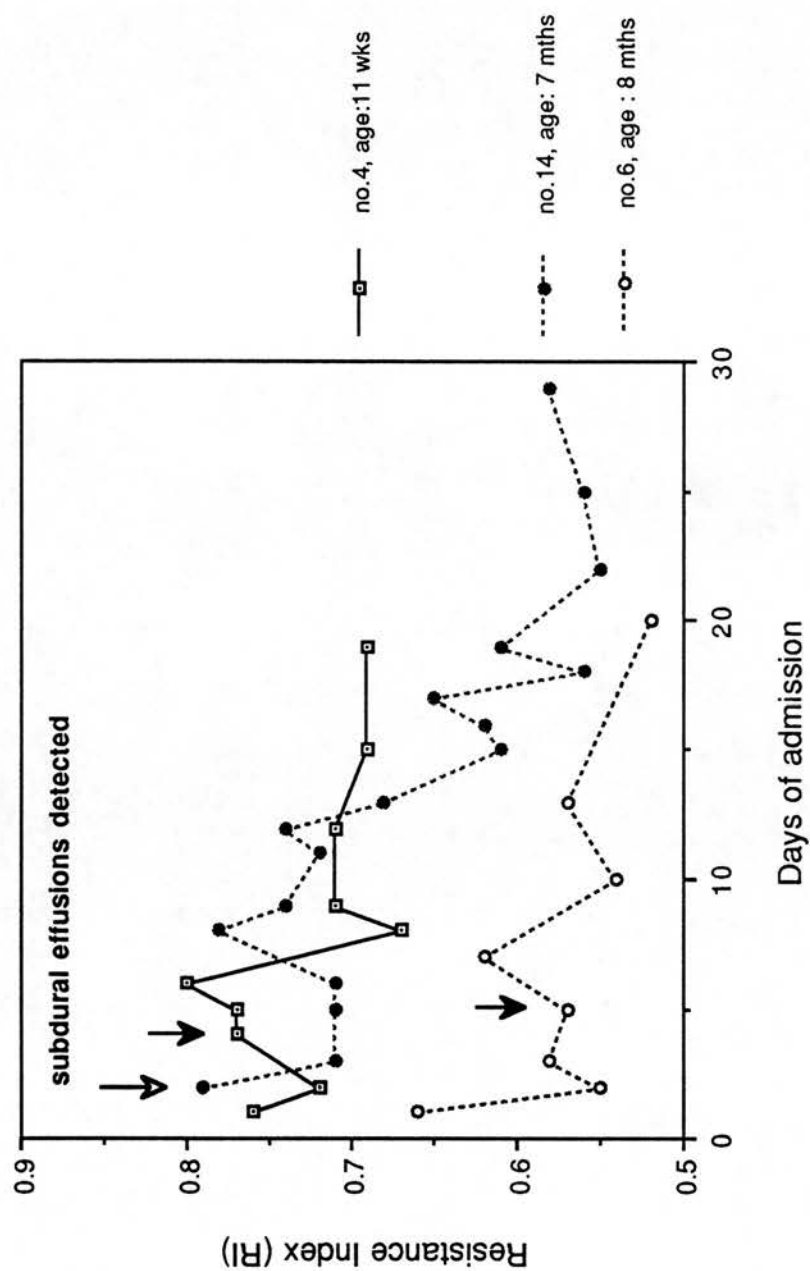


6.3.5 Subdural effusions

Three patients who developed bilateral subdural effusions were regularly monitored; Figure 6.5 shows serial RI change during their admission. Two patients who had small bilateral subdural effusions showed a subsequent increase in RI before later settling down to normal values for age. They did not require drainage or other specific treatment.

In patient no. 14, viable pneumococci were cultured from the subdural fluid obtained by subdural tap, despite adequate doses of intravenous penicillin and cefotaxime. Cranial ultrasound and CT scans showed a communicating internal hydrocephalus and bilateral subdural collections (which had persisted after a recent *H. influenzae* meningitis infection) with increased scan density of the right subdural collection. Thus 5 daily doses of intrathecal penicillin were given until cultures were negative. Serial RIs were more persistently elevated in this patient but gradually returned to normal range; MFV was less than normal range on the first day only and increased with recovery. Neurosurgical intervention was not required and he showed good clinical improvement with resolution of pyrexia and irritability. Sequelae in this patient were focal left-sided seizures which were easily controlled on phenytoin and a mild left hemiparesis which was rapidly resolving by the time of discharge.

Figure 6.5 : serial RI values in 3 patients with bilateral subdural effusions



6.4 Discussion

While the need for invasive continuous monitoring of ICP, CPP or cerebral metabolism is seldom in doubt for the very sick or comatose patients, the majority of children with meningitis, however, do not require intensive care management. However, in such children a non-invasive means for early detection of deterioration in cerebral haemodynamic trends may help in guiding optimal management. Raised ICP is still a common feature in the early phase in those who are only moderately ill (Minns et al 1989) and prompt treatment to reduce ICP eg with mannitol may help prevent further insult from reduced CPP. Some patients may develop secondary complications such as subdural effusions, hydrocephalus, or vasculitis and vasospasm and it would be important to monitor the consequent haemodynamic effects of these complications.

6.4.1 Cerebral blood flow velocity indices

An increased RI has been shown to be significantly related to raised ICP as reported by other investigators in a number of clinical conditions (Hassler et al 1988, Klingelhofer et al 1988, 1991, Chaddock et al 1991) and also in the patients with hydrocephalus as described earlier. Lundar et al (1990) have also reported from their patients who required neurointensive monitoring that in severe intracranial hypertension when CPP became critically low (below 40 mmHg), CBFV waveforms became increasingly pulsatile as systolic blood velocity increased while diastolic blood velocity was reduced. Similar findings of increased PI, decreased MFV, with diastolic velocity decreasing more than systolic velocity in association with a decrease in CPP have also been reported by Chan and colleagues (1992) in severely head-injured patients.

These results thus suggest that most of the patients with meningitis had raised ICP or reduced CPP in the early stages as initial RI was significantly elevated compared to final pre-discharge values. With recovery, final RI values decreased due to a significant increase in EDV with no significant change in PSV. The initial increased RI was mainly due to a decreased EDV, thus likely reflecting increased distal cerebrovascular resistance. This supports the view that in the initial phase raised ICP is a significant

contributing factor to compromised cerebral perfusion through increased distal cerebrovascular resistance.

Although the majority of these patients had an initial MFV within normal range for their age, there was a significant overall increase in the final values when recovered, associated with decreased RI; thus suggesting that mean CBF may have been relatively reduced initially. However, absolute values of mean flow cannot be determined by this technique and interpatient comparisons should not be made. In this clinical context, in a similar way as applied to the hydrocephalic patients, it is more reliable to utilise serial CBFV indices to chart haemodynamic trends for each individual patient.

6.4.2 Age effect (Neonates vs older infants and children)

In contrast to the differences in the pattern of CBFV changes in their two age groups as reported by McMenamin and Volpe (1984), there was no difference in the pattern of cerebral haemodynamic change between the very young infants and the older group in this study. McMenamin and Volpe suggested two possible reasons for the absence of raised ICP in the neonatal group: i) that the neonatal brain was less likely to respond to infection with oedema and ii) the neonatal cranium was more compliant. ICP in their study was indirectly measured by a transfontanometric method which could be at variance with directly measured true ICP levels. Post mortem findings on the 2 week old patient (case no. 1) in this study, previously described, illustrate on the contrary that intracranial hypertension and impaired perfusion can be equally an important complication of meningitis in very young infants. The important therapeutic implication is that careful attention to maintenance of adequate cerebral perfusion and systemic blood pressure is just as important for neonates and very young infants.

6.4.3 CBFV changes after mannitol

In all 4 patients studied there was an improvement in CBFV values after mannitol infusion. Apart from its osmotic effect in reducing brain water content, mannitol also reduces blood viscosity and increases local CBF (Muizelaar et al 1983). Decreased RI and increased MFV after mannitol

infusion suggests that cerebral perfusion was enhanced in these patients with reduction of ICP and impedance to flow.

6.4.4 Pressure-passivity

The occurrence of a pressure-passive CBFV response to systemic MAP changes only in the fatal neonatal case suggests that loss of cerebrovascular autoregulation may be a poor prognostic indicator for survival. Loss of cerebrovascular autoregulation has been reported in an experimental rabbit model with pneumococcal meningitis (Tureen et al 1990) and has been previously recognised to be an important link in the pathophysiology of intracranial haemorrhage and cerebral ischaemia in distressed premature infants (Lou et al 1979). Close attention to maintaining normal levels of systemic blood pressure is therefore required when a pressure-passive CBFV response suggests loss of cerebrovascular autoregulation.

In contrast Ashwal et al (1990) reported from their cases with bacterial meningitis that autoregulation was preserved while CBF/CO₂ reactivity varied among patients and in different regions of the brain in the same patient. Overall intact autoregulation was assumed in 18 of their patients as CBF values were normal within a range of MAP levels from 56 to 102 mmHg although only single measurements from each individual patient were plotted. With either one or two measurements only available on the majority of their patients due to limitations of repeatability with the CT- xenon technique, it may not be entirely reliable to extrapolate that autoregulation would be maintained through a similar systemic arterial pressure range in all patients. Similarly, conclusions on CO₂ reactivity in their study were based on only 2 separate measurements each in 7 patients.

Data reported by Kirkham (1991) from patients with non-traumatic encephalopathy where CO₂ reactivity was assessed by changes in MFV suggests that analysis of the shape of the CO₂ reactivity curve may be helpful in predicting poor outcome. Lundar et al (1990), also using TCD monitoring, reported 4 patients with poor outcome who demonstrated pressure passivity in addition to loss of CO₂ reactivity. Only by monitoring haemodynamic changes over a range of systemic arterial pressure and pCO₂ changes for each individual patient can we reliably be

certain of the likely cerebrohaemodynamic effects on each patient of therapeutic manoeuvres to alter these factors as there is a complex balance of hydro- and haemo-dynamic factors in each case. TCD thus provides a practical means of immediate assessment of cerebral haemodynamic CO₂ reactivity and autoregulation mechanisms in critically ill patients. Calculated CPP changes (derived from MAP - ICP) alone do not always reliably predict CBF changes; for example, hyperventilation increases CPP by reducing ICP as a result of reducing CBF through vasoconstriction. Ashwal et al (1990) highlighted the risk that increasing CPP through hyperventilation can paradoxically cause ischaemic insult when cerebral perfusion levels may already be compromised

6.4.5 Vasospasm

Vasculitis causing vasospasm or stenosis leading to further thrombotic or ischaemic damage may occur as a later complication during the acute phase. MFV values in any of the basal cerebral arteries which are markedly elevated, especially if asymmetric as reported by Bode and Harders (1989) may be suggestive. Further TCD examinations would be indicated to monitor if abnormal MFV values are persistent as alternative invasive investigations such as cerebral angiography would be highly risky in ill children. None of the patients in this study had persistently increased MFV values and thus it was assumed that none had significant large cerebral artery stenosis or vasospasm. It is not possible to be certain if the transiently elevated MFV values detected in two of the patients were due to transient vasospasm or increased mean flow but neither had any clinical signs of focal ischaemia and both patients were clinically improving. All the surviving patients had a good outcome with no serious neurologic handicap at discharge (one case with a resolving mild left hemiparesis and well controlled focal seizures). In non-hyperaemic head-injured patients with low CPP, unilateral increase in MFV was associated with noncontusion-related infarction suggesting vasospasm (Chan et al, Neurosurgery 1992). Thus as in post-subarachnoid haemorrhage and head injured patients, serial daily TCD monitoring in patients with meningitis may be helpful for detection of vasospasm or stenosis when there is significant unilaterally increased MFV.

6.4.6 Ventricular dilatation/subdural effusions

Computed tomography has a limited role in early meningitis in the absence of focal neurological signs or clinical evidence of herniation (Kline & Kaplan 1988, Haslam 1991). Changes associated with raised ICP or early cerebral oedema may not be present on early scans as illustrated by one of the patients in this study (case no. 17) and thus a normal scan may be falsely reassuring. Kline and Kaplan reported that although there were abnormal CT findings in 20 of 25 children with bacterial meningitis, the yield of information that was either diagnostically or therapeutically useful was low; positive findings of obvious clinical relevance were only present in 2 cases. It may be difficult without accompanying haemodynamic or ICP data to assess if the clinical significance of complications detected by CT or ultrasound scans such as hydrocephalus or subdural fluid collections warrant further invasive investigations or management such as surgical shunting or drainage procedures which are not always appropriate in children with bacterial meningitis (Snyder 1984). In the study patients with subdural effusions serial CBFV monitoring suggested that there was no significant perfusion compromise as RI gradually decreased to normal range. A persistently elevated or increasing RI may on the other hand be an indication for shunting or drainage procedures, as reported for the hydrocephalic patients. Subsequently the efficacy of the procedure can also be monitored with serial CBFV measurements.

6.5 Conclusion

These results suggest that serial CBFV changes provide useful information on cerebrohaemodynamic *trends* in individual children but careful interpretation of CBFV values is required for children with meningitis where the pathophysiology is complex. As TCD is a blind technique, the RI was more reliable for serial measurements performed on different days as it is of course very difficult to be certain of always placing the probe on exactly the same position or of insonating the vessel at an identical angle at every examination; thus significant error of measured CBFV change due to a variable angle of insonation can be wrongly interpreted as true flow velocity changes. In the early phase when raised ICP may be present, the RI is a more useful index and RI values >0.65 for older infants

and children and >0.8 in neonates and young infants, as seen in the hydrocephalic children, suggest that raised ICP may be causing significant perfusion compromise especially when MFV values are also less than normal.

Serial monitoring of MFV from day to day was not as consistent in this study. However, the MFV could be more useful as a means to detect and monitor complications of basal cerebral artery vasospasm or stenosis. MFV values $>120\text{cm/sec}$ may be suggestive of vasospasm (Seiler and Aaslid 1986) but repeated examinations to monitor persistence of elevated values with left/right comparisons should be made especially if focal signs are clinically detected. In the intensive care situation where a TCD probe can be left in a fixed position, MFV changes may then be a reliable guide to changes in mean volume flow over a short period for assessment of pressure-passivity or CO_2 -reactivity assuming that no significant change in calibre of the insonated vessel is likely to occur.

In summary, improvement in CBFV with decreased RI due to increased EDV, and increased MFV occurs with resolution of pyogenic meningitis. This suggests that relatively decreased cerebral perfusion may occur during the acute phase in children with meningitis who are only moderately ill. Raised ICP causing increased cerebrovascular resistance is likely to be a significant contributing factor. There was no difference in CBFV patterns of neonates or older infants and children, emphasising that equally careful attention to factors which influence cerebral perfusion is also required for neonatal patients who generally have a much poorer outcome (de Louvois et al 1991). Loss of cerebrovascular autoregulation as demonstrated by a pressure-passive CBFV response may be a poor prognostic indicator.

TCD MONITORING DURING CARDIOPULMONARY BYPASS SURGERY

7.1 Introduction

Significant advances in cardiac surgery and cardiopulmonary bypass (CPB) techniques have considerably improved the results of paediatric cardiac surgery and complex corrective surgery is increasingly attempted at earlier ages. However, as the operative mortality decreases more attention now needs to be focused on reducing the morbidity due to neurological complications and dysfunction developing in the operative and perioperative period which still limits favourable outcome in the treatment of congenital heart disease. A conservative estimated incidence of acute neurological morbidity from a survey of six major North American paediatric cardiac surgery units ranged from 2% to 25% (mean 8%) - Ferry (1990). The incidence of long-term neurologic sequelae in children remains ill defined. Furthermore, Wells et al (1983) has shown that more subtle impact on intellectual and psychomotor functioning can occur in children subjected to cardiac operations performed with total circulatory arrest (TCA) techniques. Such deficits are not usually readily apparent unless detailed psychometric assessments are carried out. A recent study (Newburger et al 1993) has also reported that a longer period of TCA during open-heart surgery in infancy is associated with evidence of greater neurologic perturbation in the early postoperative period.

There is little consensus regarding changes in cerebral blood flow and autoregulation during CPB and TCA. Henriksen et al (1983) using an intra-arterial ¹³³Xenon clearance technique to assess CBF in adult patients reported an increase in CBF during hypothermic CPB following an initial decrease during the first minute in establishment of CPB. They also reported a loss of autoregulation with a close correlation of CBF with perfusion pressure at low arterial pressures below 55 mmHg. The authors have suggested that a diffuse microvascular blockade because of emboli, thrombocyte aggregation, or stagnant capillary flow which are known to occur during CPB, could be responsible for a surrounding luxury perfusion

i.e. the brain hyperperfusion seen. Conversely, Greeley et al (1989) also using the intra-arterial $^{133}\text{Xenon}$ clearance technique in infants and children, have reported that CBF was significantly reduced during hypothermic CPB because of temperature reduction. They also showed that CBF was pressure-passive during deep hypothermic CPB. In their study cerebral reperfusion after deep hypothermia was impaired in patients exposed to a period of total circulatory arrest.

Differences in acid-base management during bypass i.e. maintaining a temperature-corrected PaCO_2 (pH-stat method) versus a non temperature-corrected PaCO_2 (alpha-stat method) of 40 mmHg may account for the reported variation in CBF data. Murkin et al (1987) have reported that CBF in the non temperature-corrected group remained independent of CPP and correlated with cerebral oxygen consumption while in the temperature-corrected group, cerebral autoregulation was impaired and flow/metabolism coupling was not maintained. However, when systemic flow rates and pressure are greatly diminished biologically significant differences between both methods of acid-base management may be small (Hindman et al 1991).

Experimental evidence from mongrel dogs has shown a significant seven-fold brain blood flow increase following the period of total circulatory arrest but microscopic cellular damage appeared in all groups with an equal degree of severity, regardless of the method of hypothermia and perfusion implemented (Molina et al 1984). There was microscopic and enzymic evidence of cellular brain damage although there were no behavioral abnormalities and no motor deficiencies observed post operatively in any of the animals. Minor neuropsychological abnormalities have been shown to be significantly more common in adult patients after CPB surgery compared to other forms of thoracic or vascular surgery (Smith et al 1986). Magnetic resonance imaging in fifteen infants and children before and after cardiac surgery showed a measurable increase in ventricular volumes and subarachnoid spaces in fourteen patients and subclinical subdural haemorrhages in five patients postoperatively (McConnell et al 1990). One-third of these patients had subclinical changes on MRI before surgery. The authors postulated that ischaemia secondary to decreased CBF during CPB surgery was a cause of

the global atrophy-like pattern observed. Significantly decreased global CBF, detected by SPECT-inhaled $^{133}\text{Xenon}$ method, has been observed up to 10 days after extracorporeal circulation (Henriksen 1984) even though none of the patients had motor deficits postoperatively. The reduction in CBF correlated positively with low MAP during bypass, duration of extracorporeal circulation and with increasing years. Thus variable degrees of brain insult can occur during cardiac surgery even though there may not be any overt clinical signs postoperatively or any specifically identifiable cause such as a prolonged period of hypotension perioperatively leading to ischaemic damage.

The pathological mechanisms through which brain insult may be mediated during bypass surgery remain largely unclear. Three primary mechanisms of neurologic injury have been suggested (Swain 1993). 'Mechanical' injury occurs from emboli which are the result of trauma to diseased blood vessels or of the intracardiac entrapment of air or particles after cardiac procedures. Microemboli are produced by interactions between blood and the artificial surfaces present in the cardiopulmonary bypass circuit. The second type of injury results from interactions in blood flow and distribution, with effects on pressure-flow autoregulation, cellular metabolism and response to reperfusion. Thirdly environmental, pharmacologic and patient-related factors may also influence the postoperative psychological state.

There is also histological evidence to suggest that gaseous emboli may contribute to the neurological deficits seen after cardiopulmonary bypass as focal dilatations have been observed in the terminal cerebral arterioles and capillaries of patients and animals who had undergone recent CPB (Moody et al 1990). Evidence of cerebral microembolism during CPB has also been demonstrated by in-vivo retinal microvascular studies using fluorescein angiography (Blauch et al 1988). Recently, magnetic resonance imaging of the brain in six patients immediately post- bypass surgery revealed visible brain swelling which subsided after the first week (Harris et al 1993). All these patients had an uneventful postoperative course with no major neurological deficit. The cause of this early cerebral swelling after bypass is unknown and cytotoxic oedema induced by microemboli, hypoperfusion or haemodilution have been postulated.

7.1.2 TCD monitoring during cardiopulmonary bypass surgery

7.1.2 (a) CBFV changes during CPB surgery

The TCD technique has also been applied to the evaluation of cerebral perfusion during CPB surgery. Lundar et al (1985) reported an increase in MCA flow velocity detected by TCD monitoring during CPB surgery. The authors related this increase to the degree of haemodilution; however, the MCA velocity changed in a pressure-passive manner with CPP in the individual patient. Increased MCA flow velocity during CPB has also been reported by von Reutern et al (1988).

Van der Linden et al (1991), however, reported a reduction of MCA flow velocity during deep hypothermic bypass to $50 \pm 4\%$ of the awake state in their patients. In their study they also demonstrated a significantly reliable correlation between MCA flow velocity compared with simultaneous thermodilution measurements of venous blood flow in the ipsilateral internal jugular vein during cardiac operations in adults. In a separate study involving six children they observed the diameter of the MCA with an electronic echo-tracking instrument connected to a real-time ultrasound scanner and showed that the MCA vessel diameter did not appear to be affected by temperature. This observation together with the reliable correlation shown with thermodilution measurements thus supports the validity of using MCA flow velocity as an estimate of changes in magnitude of volume flow through the brain during cardiac operations. In eight children during bypass surgery, they have reported that CBFV and estimated oxygen consumption decreased during cooling in proportion to the temperature decrease but surprisingly CBFV was not influenced by perfusion pressure within the range of 20 to 42 mmHg.

Temperature has been shown to have a significant effect on cerebral autoregulation, when assessed by CBFV changes during CPB surgery. Taylor and colleagues (1992) reported that cerebral autoregulation was present during normothermic CPB but was impaired or lost at nasopharyngeal temperatures between 23 and 25°C. Bujis et al (1992) also showed a close relationship between CBFV and nasopharyngeal temperatures during hypothermic CPB (18.4 - 31.9°C) and similarly found

that at lower temperatures lack of cerebral autoregulation was more common.

7.1.2 (b) Detection of microemboli by TCD

A unique clinical application of TCD monitoring during CPB surgery has been in the **detection of microemboli** to the cerebrovascular circulation (Padayachee et al 1987, Spencer et al 1990, van der Linden & Casimir-Ahn 1991 and Harrison et al 1990). Signals suggesting microemboli are high amplitude, transient signals displaying harmonic qualities with signatures clearly different from those of mechanical or electronic artefacts and causing distinct changes in the flow velocity spectrum not related to the blood flow. To the ear, these signals are harmonic in tone with a 'chirping' quality while probe motion artefacts are clearly coincident with movement of the probe and have a 'scratchy' or 'banging' quality and are bidirectional. The principle for this phenomenon is that emboli larger than the wavelength of ultrasound used (approximately 750µm for 2 MHz ultrasound) reflect sound waves and thus will produce a higher amplitude signal as compared to red blood cells (approximately 7µm) which scatter the sound waves.

Padayachee et al (1987) detected the presence of gaseous microemboli during insertion of the aortic cannula and during CPB with a bubble oxygenator. No microemboli were detected during CPB with membrane oxygenators. More recently van der Linden & Casimir-Ahn (1991) have also reported the absence of microemboli during the period of aortic cross-clamping on CPB with membrane oxygenators although scattered emboli were observed after the declamping of the aorta with the heart beating while empty as well as during the insertion of the aortic cannula and at the start of CPB. Furthermore, in patients with internal carotid artery stenosis undergoing carotid endarterectomy, Spencer et al (1990) differentiated signals attributed to formed-element emboli which they found were associated with strokes and cerebral infarction when persisting for hours postoperatively. These signals were identical to air bubble emboli but were defined as those discovered when bubbles in the bloodstream were improbable. With the use of an additional arterial line filter, Harrison et al (1990) demonstrated a highly significant reduction in the detection of microemboli at the inception and during stable CPB.

Their patients in the group with an extra filter and less recordable microemboli were less likely to show postoperative deterioration in performance on a neuropsychological test battery. Cerebral micro-embolism during CPB could thus be a contributory factor to the neuropsychological deterioration seen in some patients after CPB surgery.

The aim of this study was to assess cerebrohaemodynamic patterns during CPB surgery in children by monitoring CBFV changes with TCD ultrasonography. It was also used for detection of emboli signals at various stages of bypass and surgery.

7.2 Patients and Methods

7.2.1 Patients

TCD monitoring was performed during CPB surgery in seven patients, age range 3 years 9 months to 17 years 6 months. Their clinical details are listed below in Table 7 (i). Five patients were operated on for closure of atrial septal defect (ostium secundum), while two had closure of ventricular septal defect and one patient underwent total correction of Fallot's Tetralogy.

Table 7 (i) Clinical details of patients undergoing cardiac surgery

Patient	Age	Operation
AS	17 yr 6 mth	closure of atrial septal defect
CA	12 yr 4mth	closure of ventricular septal defect
KP	14 yr 11mth	closure of ventricular septal defect
RL	3 yr 9mth	total correction of Fallot's Tetralogy
BMcG	5 yr 3mth	closure of atrial septal defect
PMcA	7 yr	closure of atrial septal defect
JB	6 yr 8mth	closure of atrial septal defect

7.2.2 Methods

The patients were premedicated with diazepam and/or diamorphine. Anaesthesia was generally induced with sodium thiopental and

vecuronium and patients were ventilated with a nitrous oxide/oxygen mixture, initially through a face mask before endotracheal intubation. Anaesthesia was maintained with a fentanyl and vecuronium infusion. Nitrous oxide was discontinued at cannulation of the heart for bypass and the patients were ventilated with 100% oxygen or oxygen/air mixture. During complete bypass perfusion, the lungs were deflated and patients were ventilated with a flow of 2 - 3 litres of oxygen/minute via a continuous positive airway pressure circuit at a pressure of 2 - 3cm H₂O. Blood pressure was continuously monitored through a femoral or radial arterial line and central venous pressure through the right internal jugular vein. Oesophageal and rectal temperature probes were used for continuous temperature monitoring. Arterial blood gas and haematocrit analyses were carried out at intervals. Arterial blood gases were analysed using alpha-stat methods of acid-base management that consisted of analysing the blood at 37°C, uncorrected for body temperature.

SciMed membrane oxygenators (SciMed Life Systems Inc., Minneapolis, U.S.A.) without arterial filters were used during CPB. The oxygenator was primed with either a mixture of whole blood and Ringer Lactate solution (in the four younger patients) or with Hartman's solution. Cardiopulmonary bypass was established through two venous cannulae with pump return to the ascending aorta. The arterial line was carefully deaired before CPB. Caval snares and a left ventricular vent were employed. After establishment of CPB, the aorta was occluded by cross-clamping. The myocardium was cooled by perfusion of St. Thomas's cardioplegic solution No. 1 through the lower ascending aorta. Patients were cooled to moderate hypothermia only (range of minimum oesophageal temperatures 24.7- 34.2°C). The total period of aortic cross-clamping and CPB were noted. During the non-pulsatile state, MAP was usually maintained between 25 - 45 mmHg. It was aimed to maintain the patients' pCO₂ levels between 3.5 - 5.5 kPa and their pH levels between 7.3 - 7.45.

TCD monitoring of the right MCA, as previously described, was performed using a hand-held probe after induction of anaesthesia; at regular 5 - 10 minute intervals and more frequently during any specific procedure such as insertion and removal of venous and aortic cannulae for bypass, going

on or off bypass and release of arterial clamps. Simultaneous blood pressure, temperature or procedural data were voiced over onto tape.

MFV values from each patient at specific stages perioperatively were obtained i.e. 1) after induction of anaesthesiae, 2) at commencement of bypass, 3) during hypothermia, at the minimum recorded oesophageal temperature, 4) just after bypass with return of pulsatile flow, 5) at completion of surgery, 6) during the post-operative period in intensive care (within a maximum of 6 hours after surgery).

7.3 Results

7.3.1 MFV changes during separate stages of surgery

The total duration of bypass perfusion ranged from 33 - 139 minutes and the duration of aortic occlusion ranged from 13 - 79 minutes (Table 7. ii). Figure 7.1 shows the serial MFV values of each individual patient during the six stages described above. Taking the individual's MFV and MAP values at the first stage after induction of anaesthesiae as the baseline (i.e. 100%), the relative MFV and MAP percentage values from each patient at the subsequent stages are tabulated in Table 7 (ii). The actual individual MFV and MAP values at baseline (i.e. 100%) are shown within brackets.

Compared to the baseline values after induction of anaesthesiae there was a decrease in MFV% values in all but one patient (AS) just after commencement of bypass, which was accompanied by a fall in MAP % values. Figure 7.2. shows the serial mean (\pm standard error of mean) MFV and MAP% values, expressed in percent of individual baseline values, from these six patients at the six stages as described, with the MFV and MAP% values from patient AS shown separately. In these six patients the MFV% values further decreased and were at their lowest during the stage of hypothermic bypass although there was less further change in MAP % levels. Overall, mean MFV value at commencement of bypass was 82% (range 65 - 117%) of baseline values after induction of anaesthesiae while mean arterial blood pressure was 68% (range 46 - 119%) of baseline MAP levels. The overall mean MFV value further dropped to 65% (range 46 - 118%) of baseline values during hypothermic bypass while mean MAP value was 59% (range 43 - 70%) of baseline. From paired

analysis (Wilcoxon signed rank test) the decrease in MFV% and MAP% from the initial stage to the start of bypass was statistically significant; MFV% ($p = 0.02$), MAP% ($p < 0.02$). The decrease in MFV% ($p < 0.02$) and MAP% ($p < 0.04$) from the start of bypass to hypothermic bypass was also statistically significant.

After coming off bypass with return of pulsatile flow, MFV values increased to baseline levels as arterial blood pressure and temperature increased. Mean MFV% was 110% (range 77 - 148%) while mean MAP% was 87% (range 59 - 121%). The increase in MFV% and MAP% values after bypass was again statistically significant compared to values at the start of bypass ($p = 0.02$) and values during hypothermic bypass ($p < 0.01$). There was no significant difference in the MFV and the MAP values at the induction (pre-bypass) stage compared to the post-bypass stage.

MFV values from patient AS remained higher than baseline level throughout surgery as well as during the postoperative period as this patient became hypertensive during and after surgery. He required intravenous triadil and sodium nitroprusside infusion to lower his arterial blood pressure. MAP after induction of anaesthesia was 62 mmHg, rising to 95 mmHg after sternotomy, and remaining relatively high during bypass (range 24 - 75 mmHg) and rising again after surgery. Serial MFV and MAP% values from this patient are also shown in Fig 7.2 for comparison. He only required anti-hypertensive therapy till the second post-operative day. At discharge he remained normotensive without requiring any specific therapy and had no other significant post-operative problems. There was no clear explanation for this patient's raised blood pressure response during cardiac surgery as distinct from the other six patients.

Table 7 (ii) MFV% and MAP% levels during cardiac surgery

Patient	Duration of CPB	Duration of aortic occlusion	Initial		start bypass		hypothermic bypass		off bypass		surgery completed		post-operative: ITU	
			MFV (mins)	MAP (mmHg)	MFV (cm/sec)	MAP (mmHg)	MFV (%)	MAP (%)	MFV (%)	MAP (%)	MFV (%)	MAP (%)	MFV (%)	MAP (%)
AS	53	28	100% (38)	100% (62)	117	119	118	98	138	121	110	131	153	187
CA	85	50	100% (67)	100% (66)	65	58	53	50	148	103	140	100	79	114
KP	139	79	100% (79)	100% (51)	75	59	63	57	87	102	86	92	117	139
RL	103	69	100% (84)	100% (60)	76	46	52	43	104	73	122	93	56	95
BMcG	33	13	100% (63)	100% (68)	95	71	63	44	123	78	124	10	71	93
PMcA	42	19	100% (91)	100% (69)	63	46	46	51	90	59	60	83	84	90
JB	45	14	100% (52)	100% (50)	83	80	59	70	77	76	103	128	98	128

MFV and MAP levels from each patient at six stages of CPB surgery expressed as %values taking each individual's level after induction of anaesthesia, the initial stage, as baseline level (100%). Stages reported are at induction of anaesthesia, at the start of CPB, at the minimum oesophageal temperature recorded during non-pulsatile perfusion, after bypass with pulsatile flow re-established, immediately after completion of cardiac surgery and in the post-operative recovery period in intensive care.

Figure 7.1 : serial MFV values from individual patients during 6 stages of cardiopulmonary bypass surgery

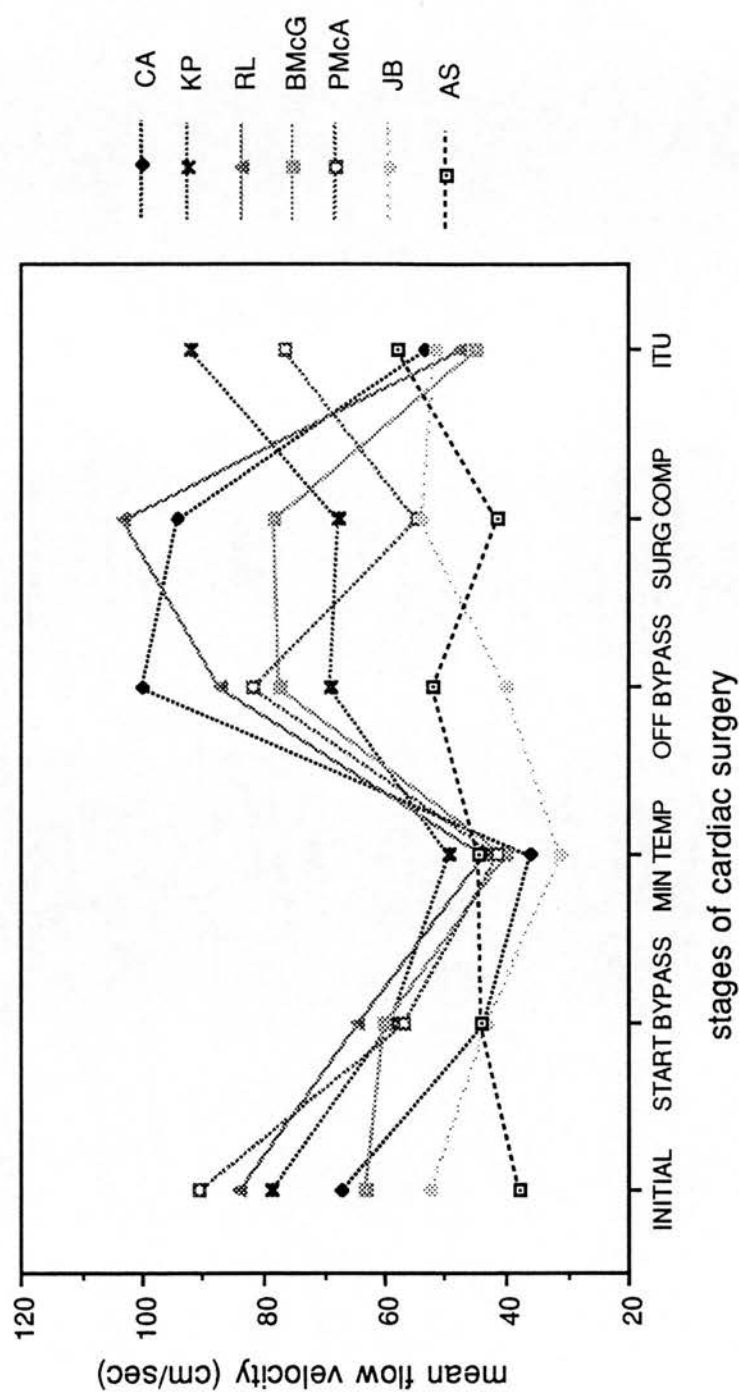
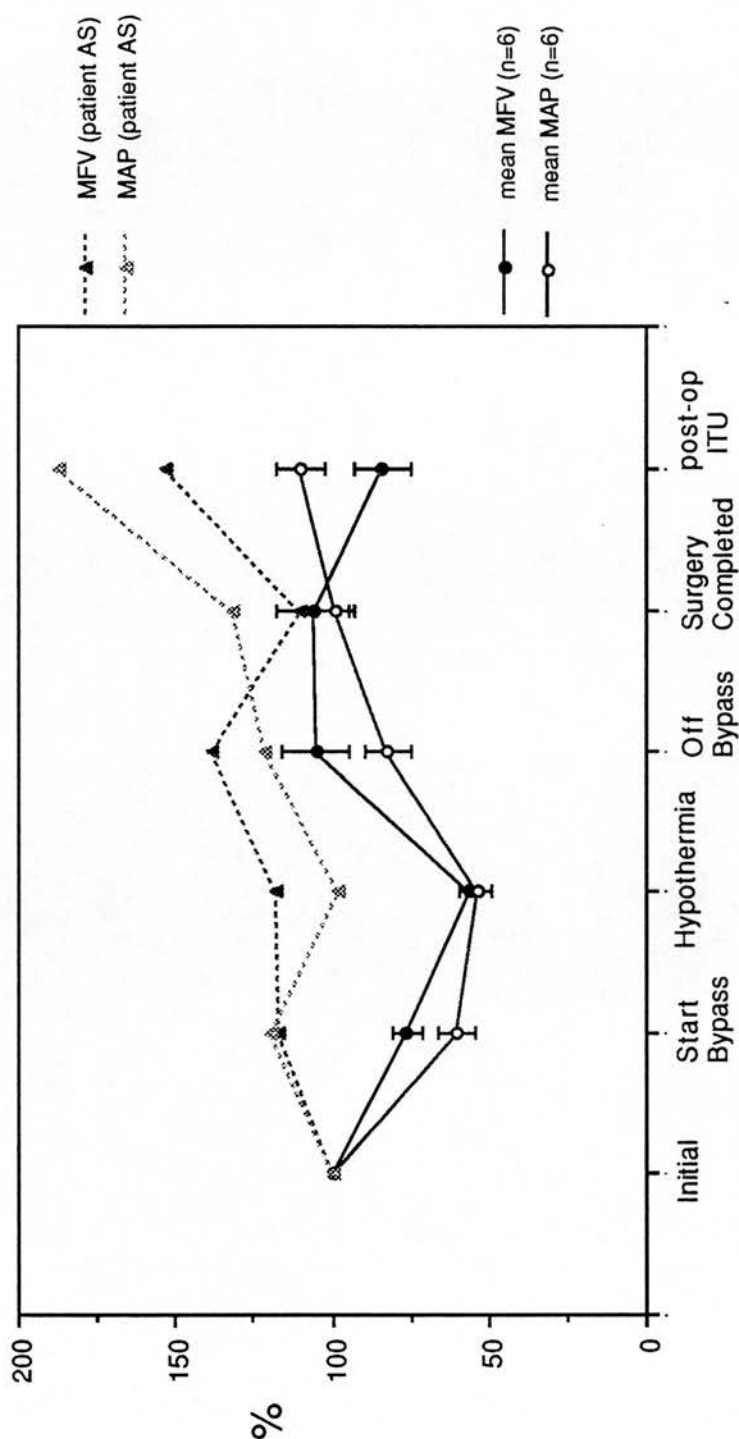


Figure 7.2 : serial mean MFV % and MAP % values from 6 patients (expressed as percentage of individual baseline value at induction of anaesthesia) during 6 stages of surgery. Percentage values from patient AS shown separately.



7.3.2 CBFV Pressure-passivity

The MFV% values were plotted against MAP% values from all seven patients at the start of bypass, during hypothermic bypass and after bypass, as shown in Figure 7.3. The initial, baseline values in all patients is represented by the 100% value on both axes. There was a significant linear correlation between the MFV% and MAP% values ($r = 0.83$, $p < 0.001$).

Figures 7.4, 7.5, 7.6, and 7.7 show plots of simultaneous MAP and MFV values measured simultaneously during CPB surgery in patients PMcA, JB, KP and BMcG; the period while on non-pulsatile CPB is indicated between the arrows. It illustrates generally that the trend of MFV values from the MCA reflect the systemic MAP trends throughout the whole procedure beginning with the induction of anaesthesia. The mean (sd) individual correlation coefficient between MFV/MAP values throughout anaesthesia and surgery was 0.75 (0.20). The correlation was weakest in patient AS ($r = 0.33$) who was hypertensive, requiring intravenous triadil and nitroprusside infusion during and after surgery. Figure 7.8 shows the simultaneous MFV and MAP values from this patient. MFV values from this patient in the earlier stages also reflect trends in the MAP values and it is only in the later stages after triadil (a vasodilatory agent) is given and in the postbypass phase when a sodium nitroprusside infusion was also required where changes in MAP are less well reflected by similar changes in MFV.

There was however, insufficient data on temperature changes to be able to examine directly the relationship between CBFV and temperature, or for multiple regression analysis of temperature effects on the relationship between MFV and MAP in individual patients.

7.3.3 Effect of pCO₂

In these patients, the aim was to maintain normocapnic pCO₂ levels throughout surgery and thus the effects of varying pCO₂ levels on MFV values during bypass were not specifically examined. It is well recognised that cerebral blood flow velocity values are considerably dependant on pCO₂ level in a similar relationship to its effect on cerebral blood flow (Markwalder et al 1984, Kirkham et al, 1986). By using accepted formulae

for calculating the corrected velocity at a $p\text{CO}_2$ of 40 mmHg (Markwalder et al 1984), the effect of variable $p\text{CO}_2$ levels on the measured MFV values during surgery can be minimised. Corrected MFV values were calculated for measurements made at the time arterial blood gases were checked before, during and after bypass perfusion. Corrected MFV values (at a $p\text{CO}_2$ of 40 mmHg) during bypass also decreased significantly ($p < 0.01$) compared to pre-bypass values, closely mirroring the change in the corresponding MAP values ($p < 0.01$). There was also no significant differences between the $p\text{CO}_2$ levels in the patients at the pre-bypass and the bypass stages. Thus in this study the $p\text{CO}_2$ levels did not change significantly to account for the observed significant changes in the MFV values during the initial, bypass and hypothermic bypass stages.

Figure 7.3 : correlation between MFV % and MAP % values from 7 patients during cardiac surgery.
(Values are calculated as percentages of each individual patient's baseline values at induction of anaesthesia.)

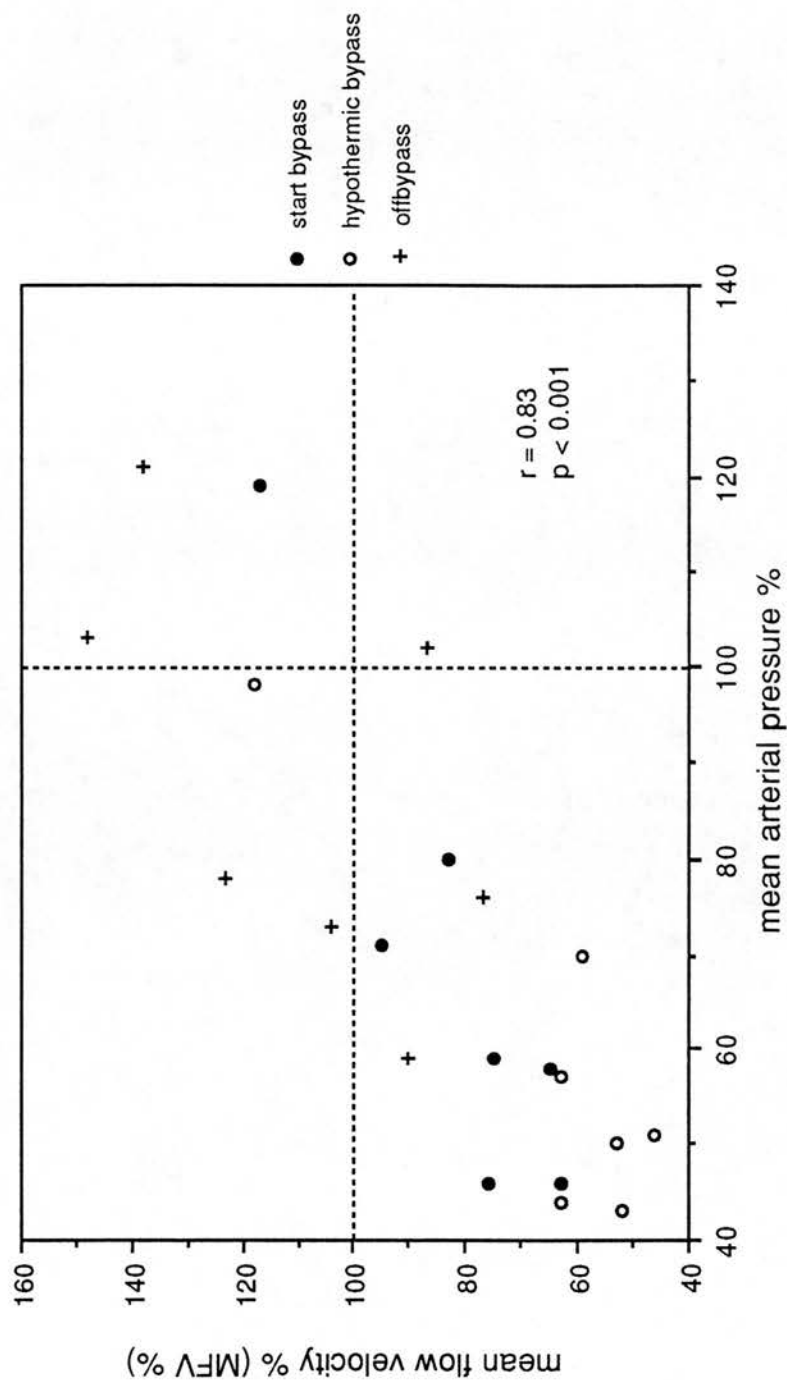


Figure 7.4 : simultaneous MFV and MAP values from patient PMcA during cardiopulmonary bypass surgery

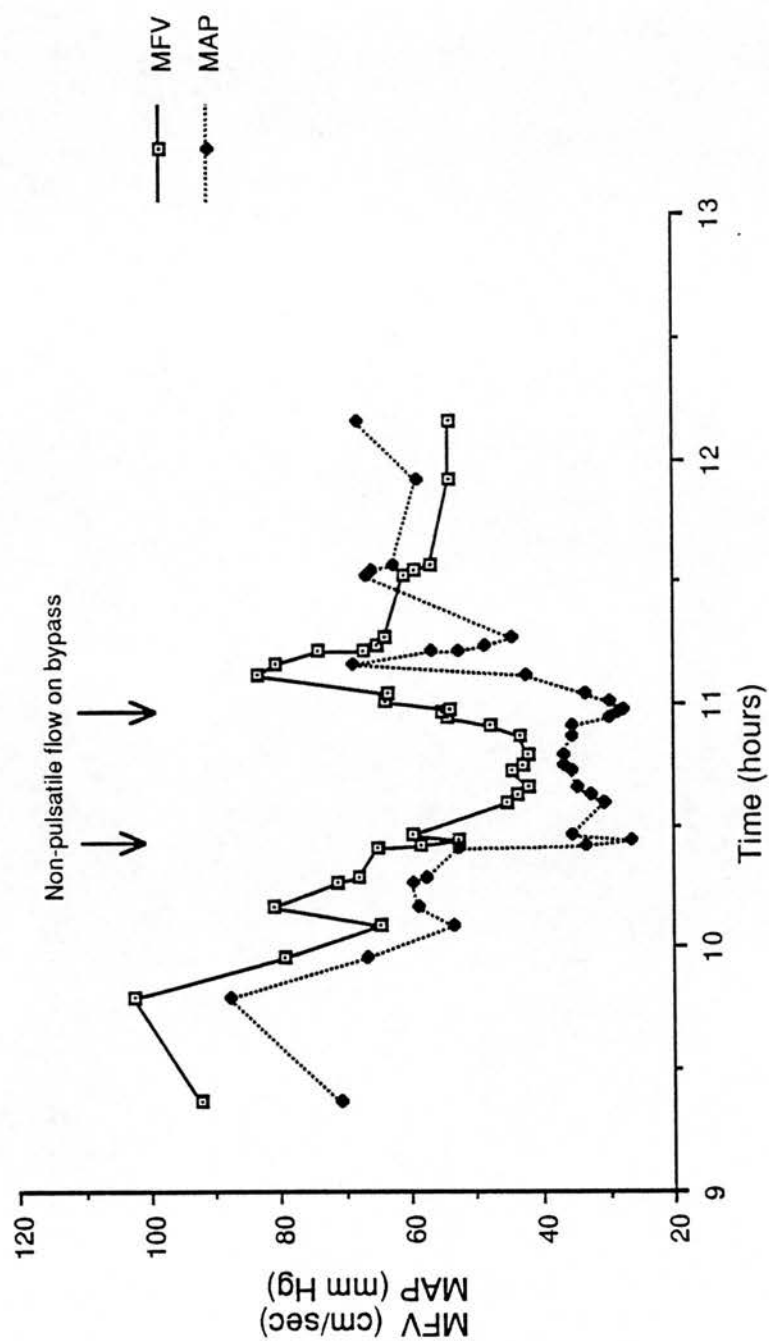


Figure 7.5 : simultaneous MFV and MAP values from patient JB during cardiopulmonary bypass surgery

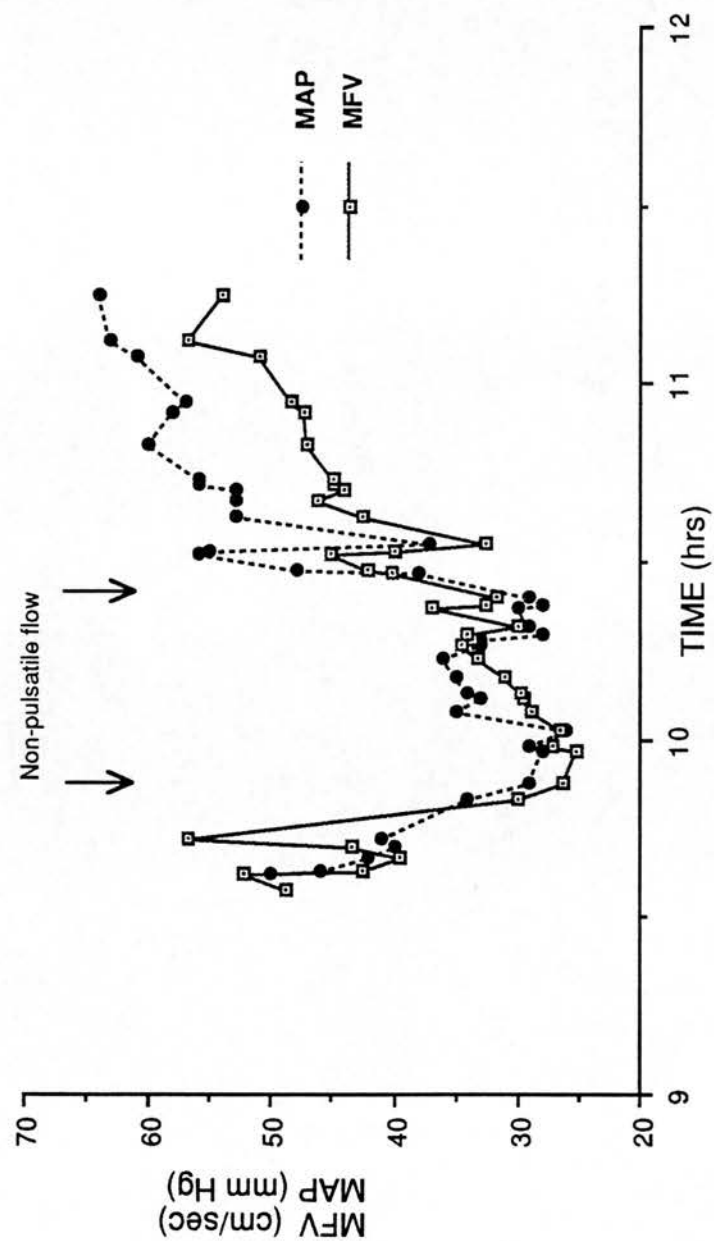


Figure 7.6 : simultaneous MFV and MAP values from patient KP during cardiopulmonary bypass surgery

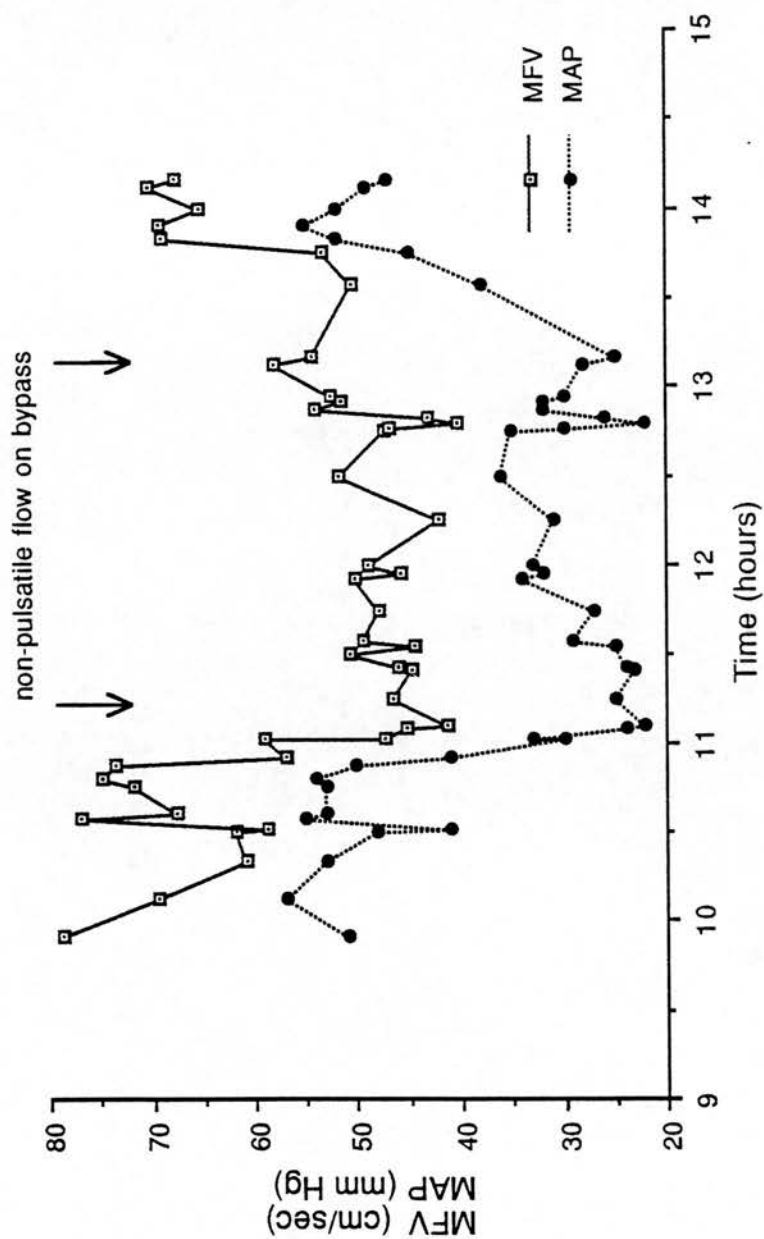


Figure 7.7 : simultaneous MFV and MAP values from patient BMcG during cardiopulmonary bypass surgery

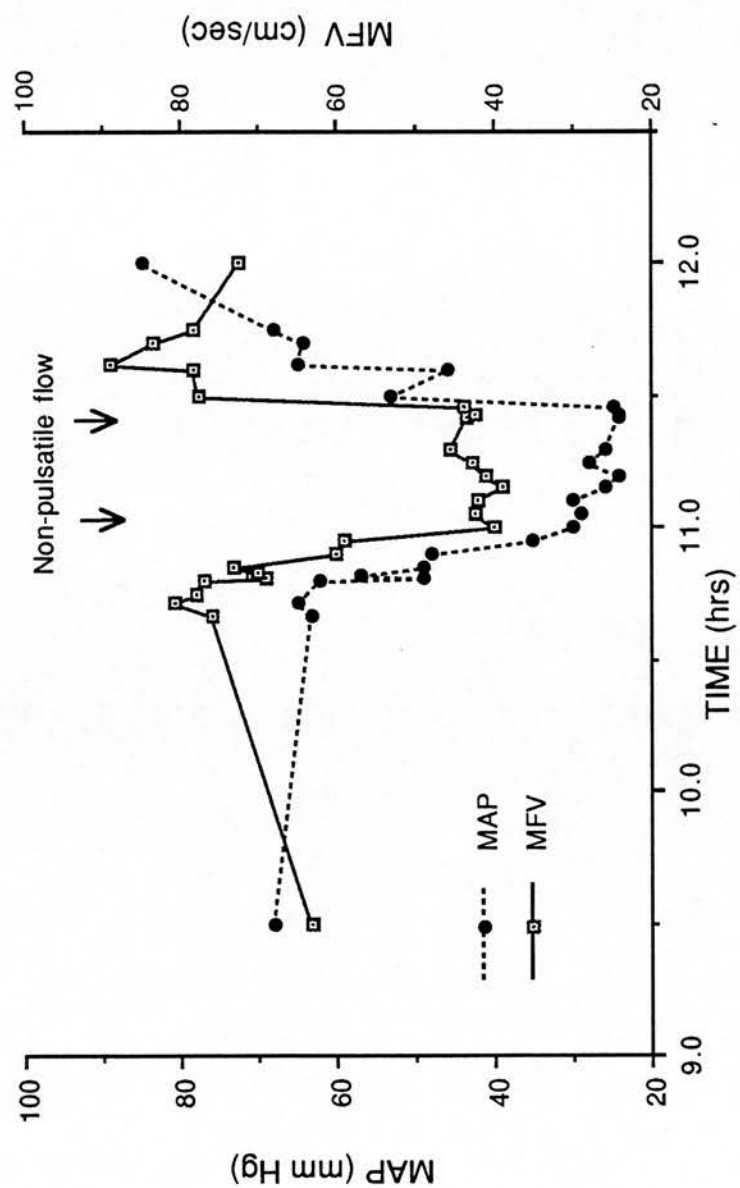
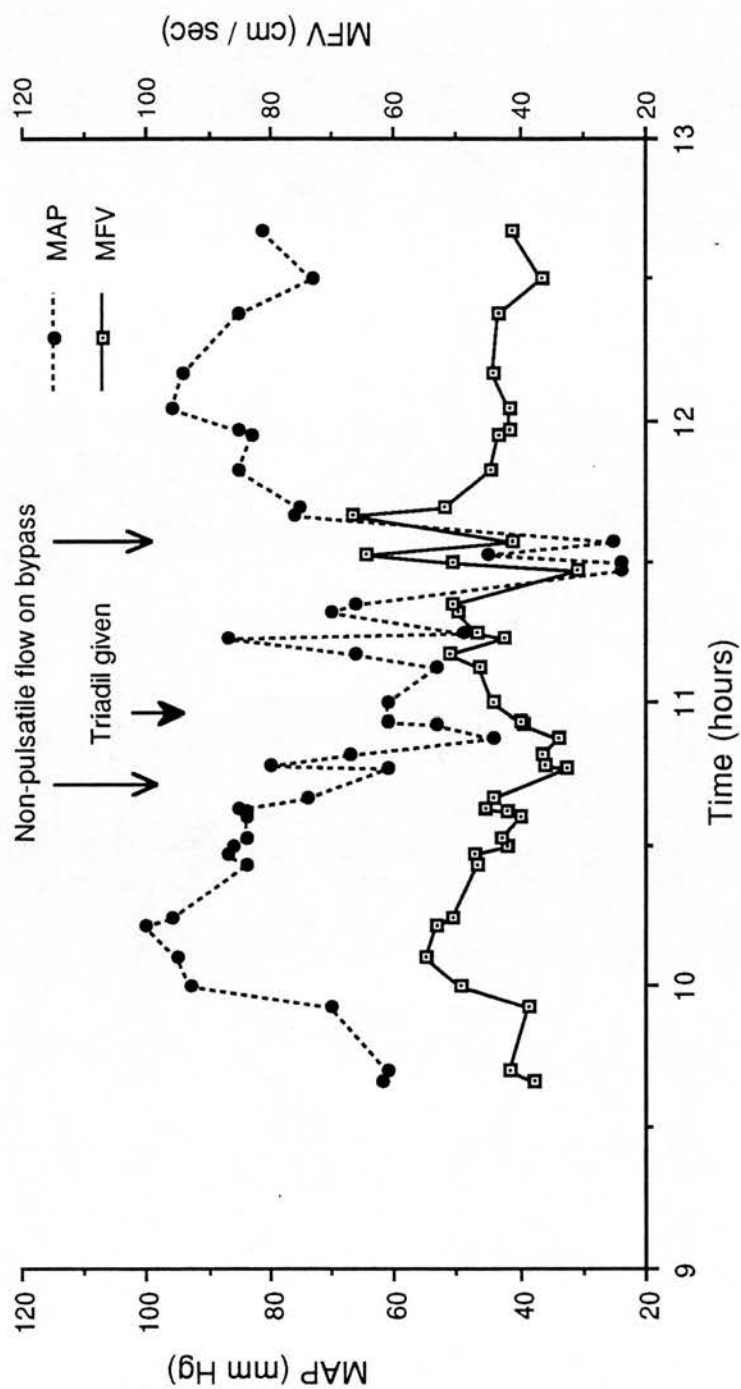


Figure 7.8 : simultaneous MFV and MAP values from patient AS during cardiopulmonary bypass surgery



7.3.4 Effect of haematocrit

At commencement of bypass perfusion, there was a decrease in haematocrit in all patients which was statistically significant ($p < 0.01$): mean (sd) pre-bypass haematocrit - 0.38 (0.04), mean haematocrit at start of bypass - 0.25 (0.04). A fall in haematocrit would, however, by itself in patients not on bypass, be expected to produce an increase in MFV rather than the decrease in MFV actually observed in six of the patients in this study.

7.3.5 Detection of microemboli

Transient high-amplitude signals displaying harmonic qualities suggestive of microemboli, as previously described, were detected during surgery in all 7 patients. These signals were unidirectional with the flow of blood and were clearly distinct from noises due to probe motion, diathermy or artefact. Figure 7.9 shows a spectrogram during non-pulsatile flow with a single microemboli signal. In three patients a few brief high-amplitude signals were recorded during insertion of the venous cannulae or following injection of heparin into the venous line prior to bypass (Figure 7.10). All patients in this study had septal defects (atrial or ventricular) which thus could have allowed shunting from the venous to the arterial circulation. Microemboli signals were also detected during aortic cannulation prior to bypass in 4 patients (Figure 7.11). In general no microemboli signals were detected while on nonpulsatile bypass perfusion except for a few very transient signals during cardioplegia in four patients when cardioplegia solution was infused through a needle puncture in the aortic root.

At the end of bypass perfusion, there was a marked 'shower' of microemboli signals in all 7 patients following the release of the aortic clamp (Figure 7.12). Removal of cannulae in particular the aortic cannula was also associated with microemboli signals. In two patients (RL, AS) there were persistent though infrequent scattered microemboli signals for a considerable period after the release of the aortic clamp and the removal of the aortic cannula while further procedures to complete surgery such as diathermy and closing up the thoracic cavity were being performed. These later procedures thus did not directly involve any puncture of the arterial circulation and would not have been responsible for any further

introduction of microemboli at this stage. The shower of microemboli signals after declamping of the aorta and these persistent signals suggest that despite the standard careful deairing procedures performed in all the patients, microemboli could have been formed as blood is redistributed from the heart-lung bypass machine to the empty beating heart.

None of these 7 patients had any clinically detectable neurological deficits following surgery and all had an uneventful postoperative recovery period. One patient (KP) had a further cardiac bypass operation a month later for aortic root reconstruction. At out-patient reviews subsequently all have remained free of clinically detectable neurological sequelae. However, no detailed psychometric assessments were done either pre- or post-operatively and it is not possible to be certain if there may not have been any subtle impact on cognitive and psychomotor function.

Figure 7.9 Single microembolus signal detected during non-pulsatile flow on cardiopulmonary bypass.

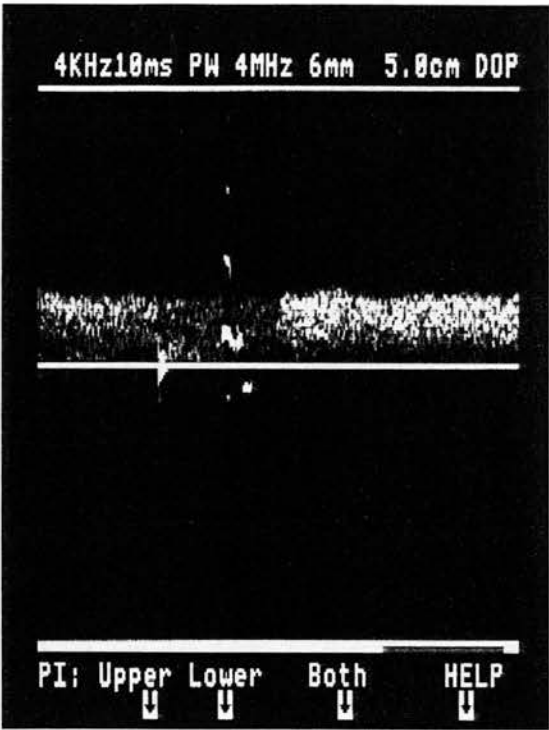


Figure 7.10 Multiple microemboli signals detected in the MCA shortly after intravenous injection of heparin prior to commencement of bypass surgery in patient with an atrial septal defect.

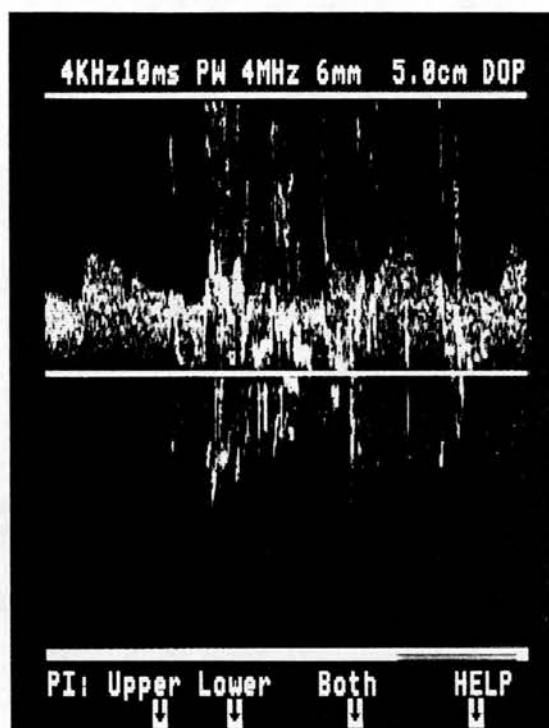


Figure 7.11 Multiple microemboli signals detected during aortic cannulation in preparation for bypass perfusion.

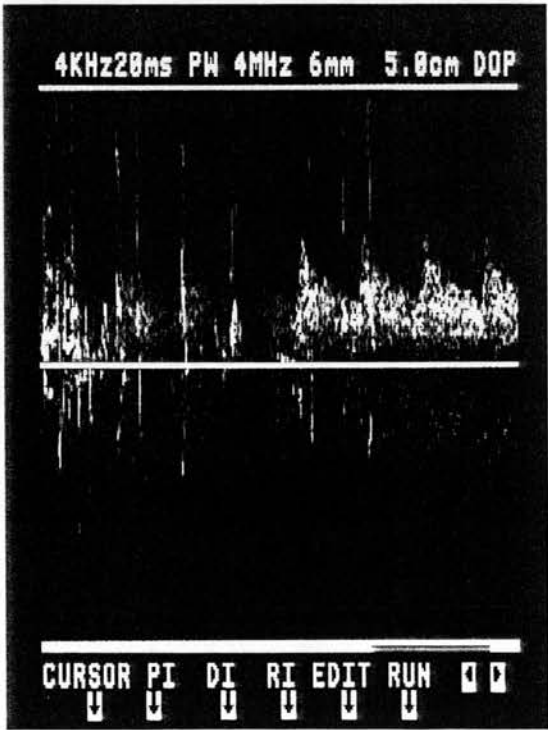
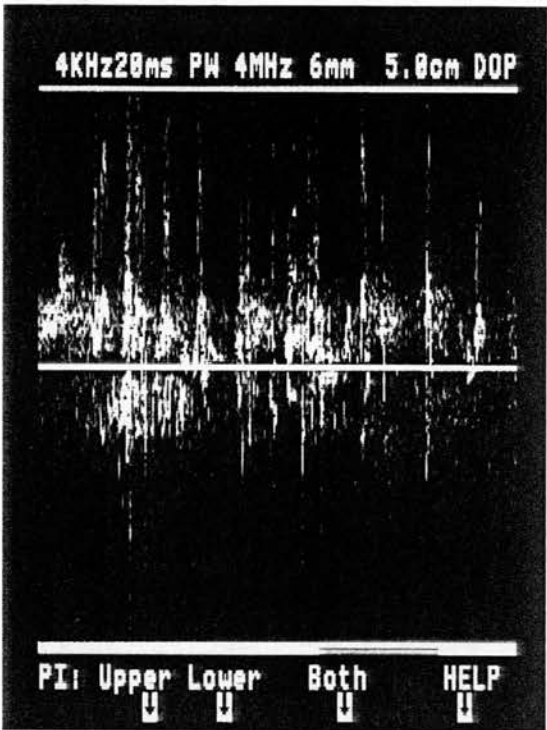
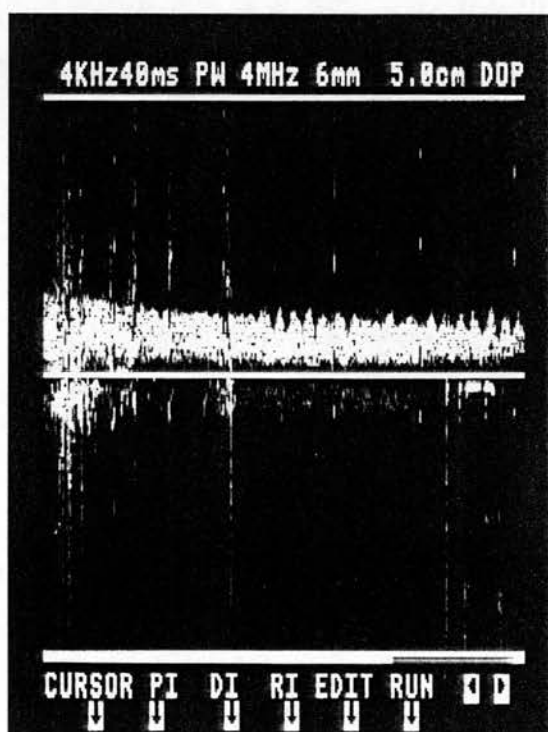
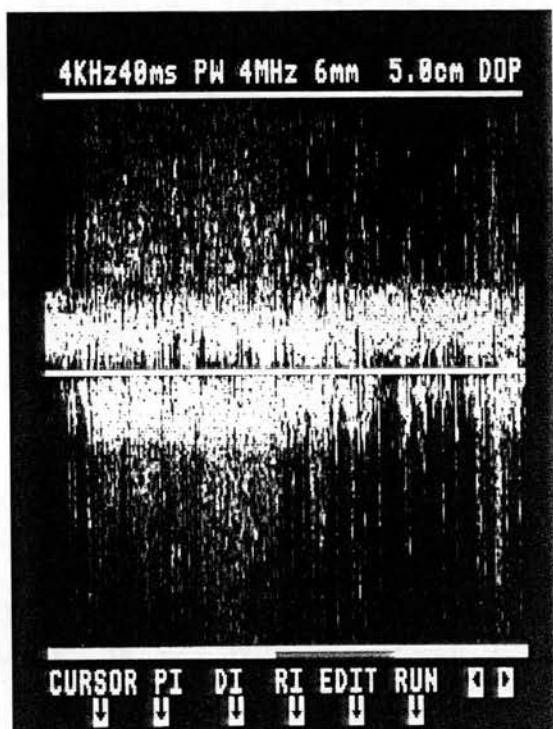


Figure 7.12 Shower of microemboli signals detected upon release of aortic cross-clamp when coming off bypass perfusion.



7.4 Discussion

During the course of cardiopulmonary bypass surgery marked changes in a number of physiological variables i.e. temperature, pump pressure, haematocrit etc are specifically manipulated to achieve a balance of optimal operating conditions and preservation of tissue perfusion which is adequate for metabolic requirements, in particular for the two organs at greatest risk i.e. the heart and the brain. Hypothermia is usually employed as low temperatures decrease the cerebral metabolic rate and oxygen consumption. Data from van der Linden and colleagues (1991) confirm the reduction of cerebral metabolic requirement for oxygen during profound hypothermia in children in keeping with the pattern demonstrated from total body oxygen consumption in humans and animal studies. Cerebral blood flow/metabolic coupling was also maintained during hypothermia in their patients.

7.4.1 CBFV changes during CPB surgery

These present results show, in common with other studies of CBFV monitoring during bypass surgery, that MCA flow velocities during CPB surgery in children were affected by changes both in the systemic arterial pressure and temperature. The changes in systemic blood pressure with commencement and completion of bypass perfusion were often mirrored by changes in MFV values in these patients, similar to the trends observed by Bujis et al (1992). The further reduction in MFV values with cooling on bypass although MAP levels were less significantly reduced, as shown in Figure 7.2, also supports findings from previous studies by Greeley et al (1989), van der Linden et al (1991) and Bujis et al (1992) that temperature has an important additional effect on cerebral perfusion. The reduction in MFV most likely reflects a reduction in cerebral blood flow with reduction of metabolic requirements during hypothermia.

However, the converse with increased perfusion or flow velocity during hypothermic bypass in adults has also been reported by Henricksen et al (1983) and Lundar et al (1985). In both these studies bubble oxygenators, which are thought to allow a greater risk of air microembolisation (Padayachee et al 1987) were used rather than membrane oxygenators. Henricksen et al (1983) had indeed postulated that the brain

'hyperperfusion' seen during cardiopulmonary bypass was suggestive of intraoperative microembolism. It may thus be possible that the disparity between these reports of increased and of decreased perfusion during CPB surgery may be due in part to the different techniques employed for oxygenation during bypass which could also influence cerebral perfusion.

7.4.2 Cerebrovascular autoregulation during CPB surgery

There is still little consensus regarding preservation of autoregulation during CPB surgery in adults or children. Some reports suggest that cerebral pressure-flow autoregulation is lost during hypothermic bypass (Greeley et al 1989, Lundar et al 1985) although this is disputed by van der Linden and colleagues (1991). Henriksen and colleagues (1986) report that in adult patients autoregulation remains operative down to arterial perfusion pressures of about 55 mmHg, but this can be abolished by pCO₂ levels >50 mmHg (6.7 kPa). These authors have also found that at low blood pressure states the CBF responsiveness to changes in pCO₂ may be abolished. However, Lundar et al (1985) found that while there was no evidence of cerebral autoregulation at CPP levels from 20 - 60 mmHg , the CO₂ reactivity was still preserved. These differing observations may in part be due to differences in temperature during CPB surgery as there is also greater likelihood of loss of cerebral autoregulation during moderate and profound hypothermic compared to normothermic bypass (Taylor et al 1992, Bujis et al 1992).

The method of acid-base management during bypass could also influence whether or not autoregulation is maintained, with loss of autoregulation more likely with pH-stat management (temperature-corrected) in comparison with alpha-stat (non temperature-corrected) management (Murkin et al 1987). Addition of CO₂ with pH-stat management techniques may cause hypercapnia-induced vasodilatation with diminished responsiveness to systemic pressure changes. However, at low bypass rates, differences between alpha-stat and pH-stat conditions are greatly reduced (Hindman et al 1991) and there is unlikely to be any biological significance or difference in clinical outcome between both techniques. In this study alpha-stat acid base management during bypass was used and thus would not be expected to contribute to loss of autoregulation.

Interpretation of the data in this study is, to a significant extent, limited by the lack of sufficient temperature data, an important variable which could have influenced the relationship between MFV and MAP differently during specific stages of bypass and this may have affected the overall observed pattern of cerebral autoregulation. Additional data would have permitted multiple regression analyses of the effects of each variable on this relationship at each specific stage of surgery.

The findings from this present study suggests that during CPB surgery the systemic or 'driving' pressure has an influence throughout on the CBFV. It is thus possible that the state of cerebral perfusion will be affected by the 'driving force' i.e the systemic arterial blood pressure even within the blood pressure ranges when autoregulation is usually expected to be fully operative, assuming a normocapnic state. Other factors such as the $p\text{CO}_2$, the degree of hypothermia will also have important additional effects on preservation of cerebral autoregulation particularly during low flow or low pressure states. The highly differing results from previous studies of cerebral perfusion / CBFV changes during bypass surgery indicate that the interactions between all these variables during bypass are highly complex. Thus during cardiac bypass surgery, it may not always be possible to assume usual 'safe' levels when autoregulation should be operative as the mechanisms of maintaining autoregulation or CO_2 reactivity may be drastically shifted by dramatic changes occurring in temperature, acid-base balance, $p\text{CO}_2$, $p\text{O}_2$, haematocrit, systemic blood pressure, change in blood pulsatility etc throughout the whole procedure. The important clinical implication is thus that close attention towards the maintenance of an adequate systemic blood pressure is very important not just during hypothermic bypass perfusion but also from the initial stage at induction of anaesthesia and throughout the surgical procedure. It is important to keep in mind that during cardiac surgery, the brain can be highly vulnerable to any sudden changes in the systemic blood pressure; in particular, abrupt systemic hypotension may not always be as adequately compensated for by cerebral autoregulatory mechanisms as presumed and may result in a mismatched or inadequate cerebral perfusion for metabolic requirements.

As none of these children suffered any clinically significant neurological deficit, it would appear that reduced cerebral perfusion with maintenance of systemic MAP between 25 - 40 mmHg during moderate hypothermic bypass was probably adequate for their cerebral metabolic requirements. However, as cerebral metabolism was not measured in this study, this remains speculative. The rapid return to baseline MFV levels on stopping bypass was also reassuring, suggesting that significant hypoperfusion was unlikely.

There was insufficient data from this study to assess the additional effect of pCO₂ levels on MFV values as the CO₂ levels were not specifically manipulated. Calculations to correct measured MFV values to a standard pCO₂ level were specifically carried out to minimise any confounding effect the slightly variable pCO₂ levels may have had on the measured MFV values. In this study the arterial pCO₂ levels during bypass also did not reach sufficiently high levels to affect autoregulation, as reported by Lundar et al (1985) and van der Linden et al (1991). When cerebral vessels are maximally dilated in response to either low arterial pressures or hypercapnia or a low pH, then variation in any of the other factors will be less likely to produce their normal response in terms of changes in CBF. It is likely that there is a complex interaction of these various factors i.e the temperature, systemic blood pressure, pH, pCO₂, and haematocrit which will influence the net cerebral perfusion during hypothermic bypass (Swan H 1984). As can be seen from the diversity of conclusions about control of cerebral perfusion during CPB surgery, it remains very difficult to generalise or extrapolate conclusions from any one individual study because the techniques of anaesthesia, bypass perfusion methods, maintenance of temperature, acid-base balance management and surgery itself vary so greatly from one study to another.

7.4.3 Detection of microemboli

This study concurs with previous reports in showing that TCD is a highly sensitive method of detecting microemboli during bypass surgery. Although membrane oxygenators are clearly much more effective in preventing microemboli during bypass perfusion itself (Padayachee et al 1987) there are still other stages of the CPB procedure when patients remain at significant risk of microemboli formation and dissemination to

the cerebral circulation. In common with previous reports this study shows that this most commonly occurs with the release of the aortic clamp, and also with insertion or removal of the aortic cannula and left ventricular vent. In addition, this study has also demonstrated that in patients with congenital cardiac lesions with septal defects, microemboli to the cerebral circulation can also occur at insertion of the venous cannulae for establishment of bypass and during intravenous injections. Indeed Chimowitz et al (1991) reported that TCD can be used specifically for the detection of right-to-left cardiac or pulmonary shunts and could thus be a helpful additional technique to increase the diagnostic sensitivity of transthoracic contrast echocardiography in patients with cardioembolic stroke or when transoesophageal echocardiography is not available or not possible.

It was not possible from these scattered signals to determine the size of the emboli detected. There was also no facility to quantify the number of emboli signals generated in each patient as there was not fully continuous TCD monitoring throughout the whole surgical procedure and no appropriate software available for this purpose during this study. However, the main observation was in confirming the occurrence of these emboli at these different stages of the surgical process. In these study patients, even in the two patients where scattered emboli signals were detected for a considerable period after the release of the aortic clamp, there did not appear to be any clinically important sequelae from these microemboli. However, as more detailed neuropsychological assessment was not performed it is thus not possible to comment on whether there may have been more subtle effects.

Clinical (Wells et al 1983) and animal studies (Molina 1984) have shown that some degree of cerebral damage can occur without any overt clinical effect. Harrison et al (1990) reported that their patients with an additional arterial line filter and less recordable microemboli during stable bypass were less likely to show postoperative deterioration on a neuropsychological test battery. It suggests that detectable neuropsychological deterioration in a proportion of patients after bypass surgery could be attributed in part to cerebral embolism. In the two patients mentioned earlier it was not possible to determine if the persistent emboli signals

could be attributed to formed-element emboli (from platelet or red cell debris) such as those reported by Spencer and colleagues (1990), whose study patients were at greater risk of developing formed-element emboli and when these were persistent for hours they were associated with cerebral infarction.

These data emphasise the importance of taking the utmost care to reduce introduction of microemboli during these vulnerable stages, such as meticulous attention to deairing procedures before release of the aortic clamp. Previous reports (Padayachee et al 1987, Spencer et al 1990, van der Linden et al 1991) are generally in agreement that most gaseous microemboli signals are usually not associated with stroke symptoms. However, the aetiology of neuropsychological deterioration after bypass surgery is probably multifactorial and the generation of multiple gaseous emboli could be an additional implicated cause. Transcranial Doppler ultrasonography could be a very useful method for evaluating new developments in bypass perfusion technology and surgical techniques aimed at reducing emboli formation.

7.5 Conclusion

Although this study reports on a very small number of patients and there is insufficient data to allow more detailed analyses or a clear conclusion on the likely interactions between a number of important variables affecting cerebrohaemodynamic control during CPB surgery, its primary intention was to serve as a pilot study to explore the feasibility and possible clinical value of TCD monitoring during cardiac bypass surgery in children. At the time when these studies were performed, there were few published reports on TCD monitoring during bypass surgery, particularly in children.

Further work will be required to clarify 'safe' levels of systemic blood pressure as well as conditions to optimise preservation of adequate cerebral perfusion and cerebral autoregulation in children at various stages of cardiac bypass surgery. However, it may be difficult to quantify 'safe' levels of CBFV indices for individuals as there is considerable normal variation, although age-related normal ranges and individual pre-operative TCD assessments will be a helpful guide. TCD offers a very

promising technique for continuous on-line assessment of cerebro-haemodynamics during cardiac surgery so that surgeons, anaesthetists and perfusionists can be made immediately aware of the effects of various procedures or manipulations on cerebral perfusion trends. As advances in cardiac surgery and bypass perfusion techniques are being rapidly made, a better understanding of cerebrohaemodynamic changes with alterations of temperature, blood pressure, pH and pCO₂ and haematocrit during cardiac bypass surgery is essential to help minimise neurological morbidity. Transcranial Doppler monitoring may help towards this and together with its unique ability for detection of emboli signals, it could be instrumental towards the achievement of safer cardiac surgery.

CEREBRAL BLOOD FLOW VELOCITY MONITORING IN HEMISPHERIC INFARCTION FOLLOWING CARDIAC SURGERY: A CASE REPORT

8.1 Introduction

Transcranial Doppler ultrasound provides a noninvasive method of serially monitoring flow velocity changes in the middle cerebral artery which may be of value in particular, in the acute phase of cerebral infarction. A number of reports (Kushner et al 1991, Kaps et al 1990, Ley-Pozo & Ringelstein 1990, Halsey & Tan 1992) have illustrated its sensitivity and reliability when compared with angiography and its value in predicting the extent of hemispheric damage which was confirmed by computed tomography. It may also have a useful role in monitoring thrombolytic treatment (Karnik et al 1992). These previous reports were mainly based on adult patients with coexistent cerebrovascular disease, predominantly of an occlusive nature. Focal neurological deficits in children can also occur following cardiac surgery but the mechanism of injury will differ from adult stroke patients and is more likely to be associated with haemorrhagic, hypotensive or embolic events during surgery. There is unlikely to be coexistent cerebral arterial disease in the majority of children. Taylor (1994) has recently described the use of colour Doppler sonography in the characterisation of alterations in regional cerebral blood flow and vascularity following acute neonatal stroke.

This report describes the cerebral blood flow velocity changes recorded from both the middle cerebral arteries in a 4 year old girl who presented with a left hemiparesis following cardiopulmonary bypass surgery for an aortic valve replacement.

8.2 Clinical details

A 4 year 7 month old girl underwent cardiopulmonary bypass surgery for an aortic valve replacement with a Bjork-Shiley valve. She had presented in early infancy with critical aortic valve stenosis and had a

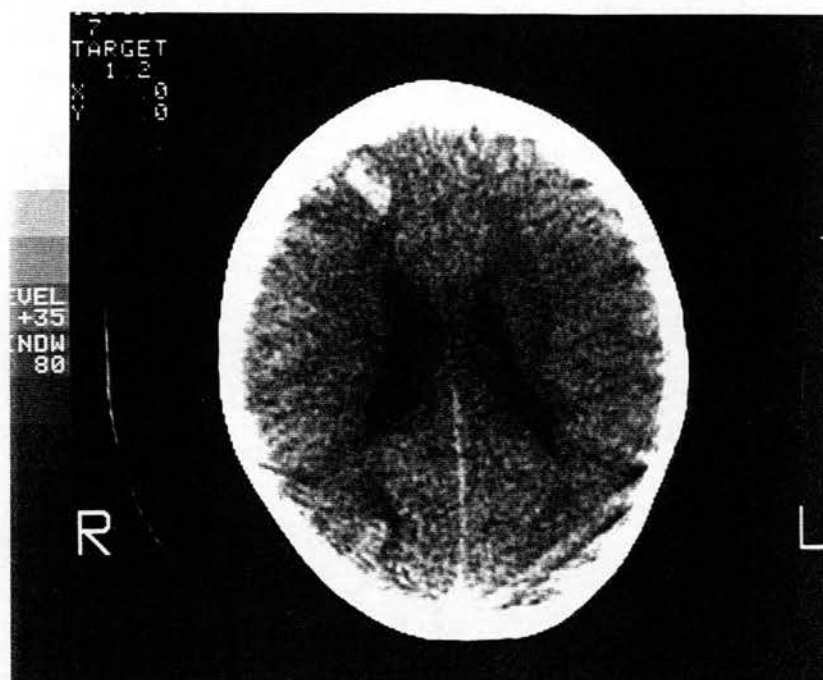
valvotomy procedure at the age of 5 weeks. She had no known neurological problems prior to her aortic valve replacement operation. There were major problems with bleeding at the beginning of the procedure on entering the myocardial tissue which was quite friable. There was relative hypotension with a systemic MAP of about 25 - 30 mmHg for approximately 30 minutes during the cooling process before hypothermia was fully established. A second period of normothermic bypass for 23 minutes was further required to control venous bleeding from behind the heart. After the surgery sinus rhythm was re-established with a good systemic arterial pressure on a small dose of dopamine. The total period of bypass perfusion lasted 176 minutes with an aortic cross-clamp period of 79 minutes. It became apparent on the same evening after surgery that she was failing to move the left side of her body. She was started on anticonvulsants prophylactically and also required a short period of isoprenaline for a period of relative bradycardia and low peripheral perfusion although she remained haemodynamically stable. Anticoagulation, initially with heparin, then followed by warfarin was also established.

Clinical examination showed a mild facial asymmetry, hemiparesis of left upper and lower limbs with increased deep tendon reflexes and an upgoing plantar reflex on the left. Fundoscopic examination showed congestion of retinal veins although optic disc margins were distinct. On her electroencephalogram, there were slow waves over the right cortex with no specific focal epileptic activity.

Transcranial Doppler monitoring was first performed at 12 hours after surgery when the hemiparesis became clinically apparent. TCD monitoring had not been carried out during surgery. Flow velocity recordings from both MCAs were performed and values were taken from optimal recordings at the same depth on subsequent days. The TCD recordings were performed at the bedside with the patient either asleep or with her cooperation in lying quietly. Corresponding blood pressure measurements were obtained with a Dinamap. She was ventilated on the first postoperative day, maintaining a normocapnic state (pCO₂ 4.88 - 5.0 kPa). Her cardiorespiratory status remained satisfactory throughout the rest of her postoperative recovery.

She remained hypotonic on her left side with little movement and indistinct speech until day 6. From day 8 she began to show gradual recovery with power returning in her left leg proximally and was able to stand with help by day 9. She continued to make steady progress and by 16 days postoperatively she had only very minimal left facial weakness and slightly indistinct speech and was able to sit up from supine unaided, stand from sitting and take a few steps with a little help. Her CT scan on day 14 (Figure 8.1) revealed multiple areas of haemorrhage with the two largest areas in the right fronto-parietal and parieto-occipital regions, the appearances suggestive of haemorrhages into watershed zone infarcts i.e. the areas between anterior/middle cerebral arteries and middle/posterior cerebral arteries' territories. At subsequent outpatient reviews she continued to show improvement with only a residual very mild hemiplegia at three months postoperatively.

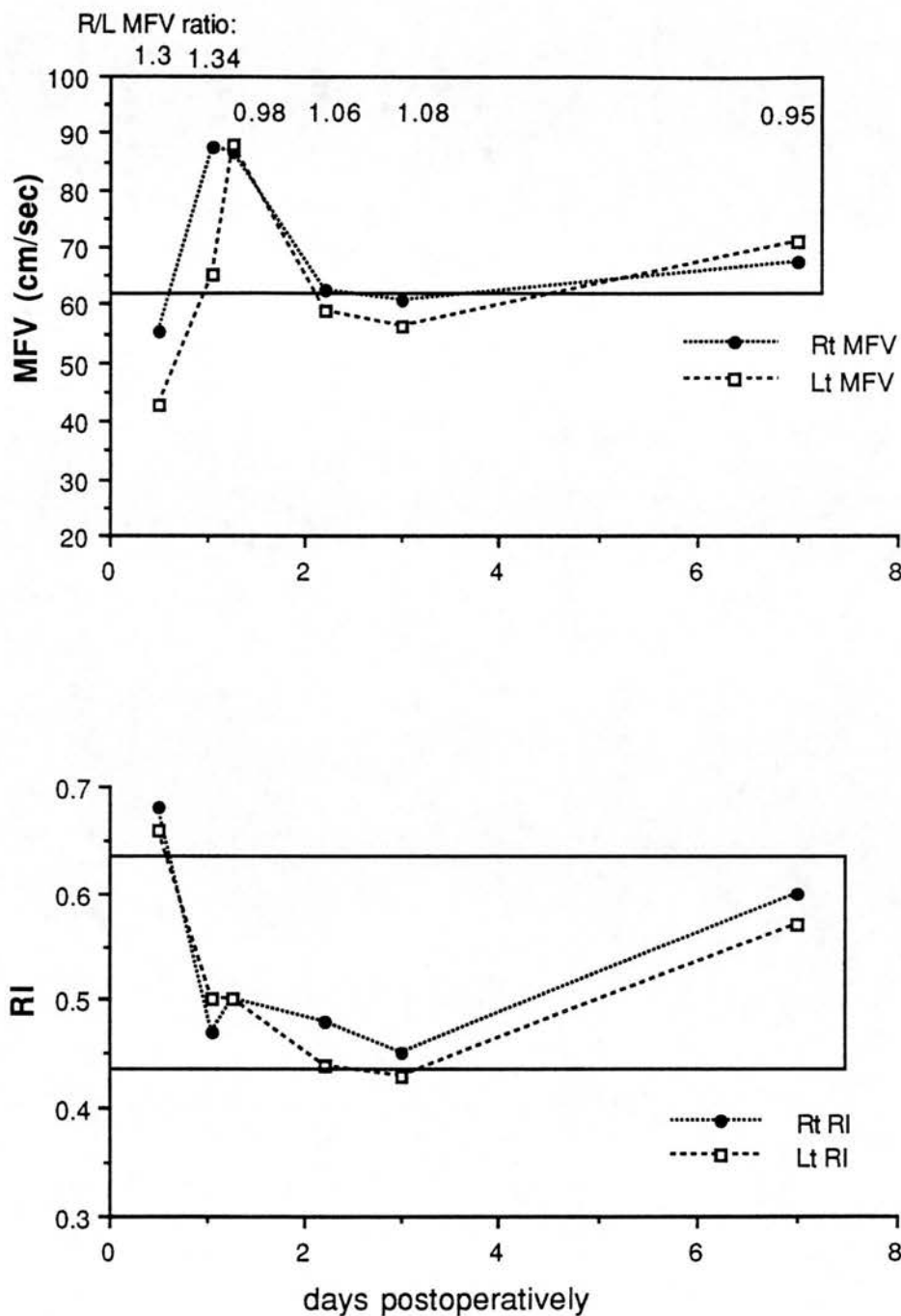
Figure 8.1: CT scan of patient who suffered a right hemispheric infarction after cardiopulmonary bypass surgery; it shows large watershed zone infarcted areas in the right parieto-occipital and fronto-parietal regions.



8.3 Results

Serial MFV and RI values from the right and left MCAs on subsequent days during the postoperative period are shown in Figure 8.2. The boxed areas show the normal ranges for MFV and RI between 3 - 6 years of age. At 12 hours postoperatively her CBFV values suggest a still relatively reduced flow with decreased MFV and increased RI values bilaterally. By 24 hours, there appeared to be improved perfusion as MFV values in both MCAs had increased while RI values had decreased to normal. Flow velocity values were maximal between 24 - 36 hours, and remained fairly constant from day 3 (52 hours) onwards. Her systemic blood pressure was in the normal range (between systolic BP: 105 - 125/diastolic BP: 55 - 85 mmHg) on all occasions when TCD recordings were performed. There was a relatively greater flow velocity, up to 34% more, in the right MCA (i.e. the post- ischaemic territory), compared to the left MCA for a period of 24 hours postoperatively. The normal side-to-side variation in MFV values in normal individuals is usually within 15%. From 30 hours postoperatively the right-to left variation in this patient was within 8%.

Figure 8.2 : serial MFV and RI values from patient EM postoperatively.



8.4 Discussion

The distribution of infarcted tissue occurring in the watershed zones in this patient suggests that haemorrhagic hypotension during surgery was the most likely mechanism of injury. Data from TCD monitoring during cardiopulmonary bypass surgery performed on the seven children as described in the previous chapter has suggested that cerebral perfusion may be vulnerable or highly sensitive to a rapid drop in systemic pressure. If the body temperature and cerebral metabolic requirements had not decreased sufficiently during the period of hypoperfusion, the brain may be at significant risk of injury from an inadequate or mismatched blood supply. Serial Doppler recordings from this patient suggests there was a period of relative mild cerebral hypoperfusion persisting bilaterally at 12 hours following injury although by 24 hours there was a relative increase in flow (relative hyperaemia), with a preferential increase to the ipsilateral (right) hemisphere. During the recovery from an ischaemic insult, rebound hyperaemia due to tissue acidosis may occur in the cerebral circulation when arterial pressure is fully restored which is then followed by a period of hypoperfusion (McDowall 1985). This period of hypoperfusion could be reflecting the generally decreased function and metabolism in neuronal tissue following an infarct (Lassen 1974) but it has also been suggested that in cases of more profound ischaemia, the continuing low global cerebral bloodflow during recovery may be contributory to the final degree of ischaemic damage (Ginsberg et al 1978).

Abnormal haemodynamic patterns were identified in 5 of 8 infants with focal ischaemic cerebral injury examined by colour Doppler sonography (Taylor 1994). In 4 infants during the acute phase (between 2 - 26 days) there was increased mean flow velocity and apparent dilatation in ipsilateral cerebral arteries and veins compared to cerebral vessels in the opposite hemisphere. This pattern was thought to represent regional luxury perfusion/hyperaemia as a result of a local increase in cerebral metabolism following hypoxic injury. However, one infant with a large right hemispheric infarct with sonographic appearances of a diffusely echogenic right cerebral hemisphere showed a markedly decreased mean flow velocity in the right MCA at day.

It is most likely that the relatively greater flow velocity to the right hemisphere in this patient which persisted for a period of up to 24 hours reflects the relative hyperaemia due to the effect of local tissue acidosis after ischaemic damage. In this patient the increased MFV was unlikely to be due to right MCA stenosis as occlusive arterial disease was not the underlying aetiology. During the period of reperfusion after focal damage it is probable that there are focal areas of varying flow adjacent to one another and changing temporally and spatially, modified in part by local tissue factors. However, TCD alone, without accompanying imaging facility can only provide some impression of hemispheric differences and will not have sufficient sensitivity to detect focal flow changes following deep lesions.

It could be argued that the observed changes in MFV do not reliably reflect changes in hemispheric flow but are the result of day-to-day variability or to due to variability in the angle of insonation at each examination. However, the changes in MFV values measured within the first 30 hours were greater than 20% variance from the more stable MFV values from the third postoperative day, which is thus biometrically significant as intraobserver variability for the MCA from day-to-day has not been reported to be greater than 10% (Adams et al 1992). This patient did not have any intracranial structural or space-occupying abnormality which would have caused significant distortion of the course of the MCA, thus there would be unlikely to be significant differences in the angle of insonation of the MCA at each examination to account for >20% variance. Within a variation of 30 degrees in insonation angle the error percentage in MFV values is up to 13%.

Previous reports based on adult patients after an acute stroke have suggested that a low MFV on the affected compared to the unaffected side was predictive of a greater size of infarcted territory (Kushner et al 1991) as well as a poor prognosis for recovery (Halsey & Tan 1992). In contrast this patient who demonstrated steady gradual recovery showed moderately increased MFV on the affected side in the initial recovery phase with fairly symmetrical flow velocities to both hemispheres by the second postoperative day. Closer examination of absolute velocity values in this patient also shows that they were not markedly different from normal ranges of MFV

values for her age group, thus there was no evidence from TCD findings of a significant state of marked hypo- or hyperperfusion globally after the infarct. However, as there is considerable inter-individual variation in absolute flow velocity values, TCD values cannot be used to reliably predict a critical perfusion threshold or indicate a state of luxury perfusion for any particular individual. The CBFV changes which occurred in this patient were illustrative of a pattern of haemodynamic readjustment after ischaemic infarction from a hypotensive insult. However, it is important to keep in mind that without other supportive cerebrohaemodynamic measurements such as CPP, arterial-jugular venous oxygen content difference or other collaborative cerebral perfusion techniques to determine the state of global cerebral perfusion, interpretation of these CBFV trends remain speculative.

The CBFV indices suggested that cerebral perfusion by 12 hours postoperatively was not critically compromised as MFV values were not markedly depressed and the RI values were also not markedly elevated. No specific aggressive intervention was thus clinically indicated at that stage. It is however, possible that earlier TCD monitoring during the acute phase, for example within the first few hours after the ischaemic insult may have revealed a more disturbed cerebrohaemodynamic pattern. However, there was no clinical suspicion of any neurological deficit at the early postoperative stage while the patient was still maintained in a heavily sedated state. Routine TCD monitoring after cardiopulmonary bypass surgery for patients in whom there is concern of risk of neurological sequelae could perhaps be helpful in early identification of disturbed cerebrohaemodynamic trends as clinical awareness of neurological complications is often delayed due to the effect of anaesthetic and sedative medication still on board. If specific 'cerebral protective' therapies are to be considered, early identification of the 'therapeutic window' period through effective monitoring may become necessary.

In adult patients after thrombo-embolic stroke, occlusion may be assumed if there is no flow in the MCA while flow in the posterior or anterior cerebral arteries can be detected from the ipsilateral temporal window. However, estimation of low flow velocity values may be prone to greater

error due to technical reasons as previously explained in Chapter 2. In these clinical circumstances further invasive investigations such as angiography followed by thrombolytic therapy, if occlusion is confirmed, may be indicated.

In neonates and young infants with a patent anterior fontanelle, duplex colour Doppler imaging could provide more useful information on focal alterations in regional CBFV after cerebral infarction. However, in older children, as in adults, TCD remains currently the only practical means of repeated, noninvasive, bedside assessment of cerebrohaemodynamic patterns after cerebral infarction. This case report is included primarily to illustrate that the TCD technique can be applied in children to demonstrate hemispheric cerebrohaemodynamic asymmetry and readjustment after hemispheric infarction. It is important though to recognise that further studies to prospectively follow-up CBFV patterns after cerebral infarction in larger numbers of children with specific causes i.e. thrombotic/ embolic, or hypotensive/haemorrhagic etc will be needed before we can fully evaluate the clinical prognostic value of CBFV recovery patterns in each separate group. TCD thus could be a promising aid in the understanding of cerebrohaemodynamic patterns and be a useful *supplementary* diagnostic tool in clinical management after acute cerebrovascular events in children as well as adults.

CONCLUSION

I have reported, in the work on this thesis, the cerebral blood flow velocity findings, as measured using the transcranial Doppler ultrasound technique, in four main clinical groups, i.e. normal children, childhood patients with hydrocephalus, pyogenic meningitis and during cardiopulmonary bypass surgery. Clearly these are four diverse groups where the physiological and pathological conditions vary considerably but nevertheless there were consistent CBFV findings which can usefully be extracted from all these groups.

The CBFV data from normal children in this study and other studies reported in the literature show a remarkable consistency in the pattern of change with age and also in the actual range of values reported. Of particular note is that after infancy the RI remains very stable, thus indicating that this index is useful for making comparisons among patients of different age groups. In patient groups where the ICP dynamics may be altered by pathological processes such as in hydrocephalus or meningitis, raised ICP was consistently reflected by increased waveform pulsatility with raised RI suggesting that in these patients the raised ICP was associated with increased cerebrovascular resistance to flow. In these patients recovery with a return to normal ICP levels was also reflected by normal RI levels i.e. similar to RI levels measured in normal children with no neurological problems. It is important, however, before making such an association between raised RI and increased cerebrovascular resistance to establish that in these conditions the raised RI was due to decreased end diastolic velocity and not because of an increased peak-systolic velocity as progressively increased downstream resistance leads to decreased diastolic flow velocity. The interpretation of changes seen in the RI from any clinical context is more meaningful only when associated changes in the EDV, PSV and MFV are also examined. Correlation between RI and ICP between individuals is more reliable outwith the infancy age group. However, there also appears to be a reliable correlation between RI and ICP for an individual neonatal or young infant with hydrocephalus.

The RI is clinically useful for noninvasive assessment of hydrocephalic patients whether CSF drainage or shunting is required, in those with existing shunts whether shunt blockage or malfunction is responsible for their symptoms and also for closely monitoring those left unshunted. In particular for each individual patient the RI is a reliable index for monitoring purposes, ie finding a raised RI when they present with symptoms suggestive of raised ICP is highly significant especially if a previously measured RI value obtained when asymptomatic was within the normal range. Using the volume-flow velocity response i.e. by examining the rate of change in RI with CSF volume changes may yield additional information on the state of volume-buffering reserve in these patients which could be a much more useful predictor. However, the results were too few to be conclusive but rather serve as a suggestive model for further prospective studies with larger numbers required.

In patients with meningitis, particularly those not warranting invasive monitoring and intensive care support, TCD monitoring offers a quickly available noninvasive method of assessing their state of ICP and cerebro-haemodynamics. This of course could be very helpful in guiding optimal management in the acute stages and also be of value in assessing those who develop complications such as vasospasm or stenosis, subdural effusions and hydrocephalus. Again in this clinical context the RI appears to be a more reliable index, as for serial measurements done over a number of days, it would not be reliable to assume a constant angle of insonation. However, measurements of MFV which are markedly higher or lower than normal range for age or which show marked side-to-side asymmetry could also be clinically very helpful and may indicate the need for further invasive or imaging investigations such as angiography or MRI scanning.

Much of the current research in TCD utilises the measurement of MFV as an index of mean cerebral blood flow with the accompanying intense controversy about the validity of this assumption. Clearly this will always continue to be the case when it comes to the interpretation of MFV data as the measurement of MFV will always need to be rigorously carried out, whether done with a transcranial probe fixed in position as much as possible with the help of a headband or by a handheld probe which is

regularly adjusted for optimal position by an experienced operator. The processing of continuous MFV data is also very laborious unless there is linked computerised analysis, separately from whether the raw Doppler spectral outline data is manually or automatically traced by the TCD equipment used. For clinical purposes automatic tracing and calculation of MFV from the spectral outline will be required as manual tracing would be simply too time-consuming to make this a useful tool to clinicians. Most TCD machines now provide this facility and Doppler data is also usually converted and presented in velocity units i.e. cm/sec. The Doppler data for this thesis was, as previously described, all obtained from manual tracing of Doppler waveforms which although laborious was very helpful in the interests of research accuracy because all the data, ie every single waveform had to be rigorously selected for clarity and reliability. This would have helped in achieving greater consistency because the human eye is far more accurate in tracing the spectral outline compared to an automatic processor.

Mean flow velocity data was used, in the main, only in two studies specifically, i.e. the sleep studies on the hydrocephalic patients and during cardiopulmonary bypass surgery monitoring. While recognising that hand-held probes may lead to inexact repetition of the angle of insonation and thus introduce more error in MFV measurement as compared to probes held in place with a headband, unfortunately this was not available for use during both these studies. Hence careful steps to make sure measurements were always obtained from the same position and precautions to only select optimal quality Doppler data were always taken during each individual recording over a period of a few hours. Interpretation of the data was limited to examination of *trend* changes for each *individual* patient rather than as absolute measures of flow for inter-individual comparisons. Thus within such limitations, it may be reasonable that changes in MFV indicate trend changes in mean flow for individual patients over a short period of time.

In the sleep study, it is important to stress that more information was yielded by examining both changes in MFV and RI *simultaneously* in response to the measured ICP changes. The CBFV changes seen suggest that some hydrocephalic patients have the cerebrohaemodynamic reserve

to compensate for episodic changes in ICP while those with limited intracranial compliance are less able to haemodynamically compensate during these spontaneous episodes or raised ICP. It is only possible to evaluate such patients more accurately by carrying out prolonged recordings to study the dynamic responses as single or brief recordings may not reveal much if the patient happens to be in a compensated or asymptomatic state just at that particular time.

In the cardiac bypass surgery study the measurement of waveform pulsatility obviously has little relevance, as for a considerable period of time during the period of most interest ie while on bypass perfusion, the CBFV waveform pulsatility is of course zero. In this study changes in the MFV percentage give an indication of the relative flow changes at various stages of the surgical procedure and show the close relationship to the systemic blood pressure i.e. the 'driving pump' pressure although there is insufficient data to determine the effect of other important variables such as temperature on this relationship. Other available methods of measuring cerebral perfusion would not provide such an immediate, on-line continuous measurement as is possible by the TCD technique. Its other unique contribution is the ability to detect emboli signals to the cerebral circulation and thus serves to guide more careful surgical and bypass perfusion techniques.

The case report suggests that TCD can be applied in monitoring cerebrohaemodynamic patterns in children after acute cerebrovascular events and could be helpful for therapeutic or prognostic purposes. While the use of TCD for assessment after strokes and subarachnoid haemorrhage has now become quite widely applied in adult patients there are still few reports on its use after acute cerebrovascular events in children. Further such studies in children will be required.

There are of course limitations on the clinically useful or prognostic information which can be yielded particularly by single TCD examinations. The normal velocity ranges established serve only as a guide and thus cannot be taken to represent absolute measures of cerebral perfusion especially for inter-individual comparisons. After any acute event such as an encephalopathic illness or cerebrovascular insufficiency,

if relatively 'normal' cerebrohaemodynamic balance or blood flow has been restored, normal TCD findings of course cannot provide any indication of the degree of ischaemic damage which may already have occurred. For example, although a characteristic pattern of low flow velocity waveforms with absent or reverse diastolic flow is well recognised in patients with brain stem death, these characteristic waveforms may initially not be seen till cerebral tamponade is well advanced and in the early period after the hypoxic- ischaemic insult TCD examination could well show relatively normal CBFV waveforms. Thus prognostication should still be guarded despite normal TCD findings in these circumstances. In encephalopathic patients, more detailed, repeated TCD examinations could, however, yield more useful information by assessing if cerebrovascular autoregulation or CO₂-reactivity is still preserved and this may have prognostic implication. Abnormal cerebral blood flow velocity waveforms also do not necessarily always imply abnormal cerebrohaemodynamic conditions, for example infants with patent ductus arteriosus will show CBFV waveforms with reverse diastolic flow due to the retrograde flow from the aorta into the pulmonary artery. Thus it would not be reliable to associate increased RI with increased ICP in these infants. These examples illustrate how TCD findings taken in isolation have limited clinical value but instead should be used as a contributory investigation taken together with a full clinical assessment and other relevant investigations. However, careful interpretation of CBFV data from any one study is always necessary and the extrapolation of conclusions drawn from one clinical context to another may not be valid. This should always be kept in mind when evaluating information from the numerous Doppler studies in infants and children where apparently conflicting conclusions are drawn because the patient groups and conditions are usually not similar or directly comparable.

In my experience, this technique was always readily acceptable to all parents because of its noninvasive and safe nature. It was well tolerated by young infants and children and was only on occasions not easily performed on older infants or toddlers who did not like having anything placed against their heads or would not keep sufficiently still. Transcranial Doppler equipment is relatively inexpensive and the technique can be easily learned by following well described examination

techniques so that any clinical staff can become quickly familiar with this technique which does not require any specialist e.g. radiological training. However, familiarity or experience with the technique is required to be sure that the TCD data obtained is reliable. With its advantages over other methods of assessing cerebral perfusion in bedside conditions as previously described, the TCD technique can certainly be of value to clinical paediatricians in the management of their patients.

This thesis has explored some of the clinical applications of transcranial Doppler ultrasound monitoring in infants and children and has shown that this can be a practical, noninvasive method of quickly assessing intracranial dynamics in some clinical situations. It is a useful investigation in the clinical management of hydrocephalus, meningitis and may be clinically applied for monitoring cerebral perfusion trends and cerebral emboli detection during cardiopulmonary bypass surgery. Careful interpretation of TCD findings, however, is *always* necessary. There is also scope for more research into further clinical applications of the TCD technique in children such as in traumatic and nontraumatic encephalopathy, after ischaemic or haemorrhagic cerebrovascular events, with haematologic disorders such as sickle cell anaemia and in other clinical conditions where cerebrohaemodynamic control may be affected.

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Appendix 1

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Permission has been sought and granted by Springer-Verlag, Tokyo and from my joint authors to allow photocopies of the following publication:

Minns RA, **Goh D**, Pye SD, Steers AJW. A Volume - Blood Flow Velocity (VFR) relationship derived from CSF compartment challenge as an index of progression of infantile hydrocephalus. In: Matsumoto S, Tamaki N (eds) Hydrocephalus: Pathogenesis and Treatment. Springer Verlag Tokyo, Berlin, Heidelberg 1991; 270-278.

to be included in this thesis.

Appendix 2

PRESENTATIONS AND PUBLICATIONS

The work carried out for this thesis have been presented at the following scientific meetings:

1. 1st International Conference on Hydrocephalus: Kobe, Japan, November 1990.
2. 22nd Annual Scientific Meeting of the British Medical Ultrasound Society: Harrogate, December 1990.
3. European Federation of the Child Neurology Societies: Paris, France, February 1991.
4. 17th Annual Meeting of the British Paediatric Neurology Association: Newcastle upon Tyne, January 1991.
5. 35th Annual Scientific Meeting of the Society for Research into Hydrocephalus and Spina Bifida: Liverpool, July 1991.
6. Consensus Conference on Pediatric Neurosurgery: Assisi, Italy, April 1992.
7. VIII Intracranial Pressure Symposium: Rotterdam, Netherlands, July 1992.
8. 24th Annual Scientific Meeting of the British Medical Ultrasound Society: December 1992.
9. 19th Annual Meeting of the British Paediatric Neurology Association: London, January 1993.

The following papers relating to the work carried out for this thesis have been accepted for publication:

1. **Goh D**, Minns RA, Pye SD, & Steers AJW. Cerebral Blood Flow Velocity changes after ventricular taps and ventriculoperitoneal shunting. *Child's Nervous System*. 1991; 7: 452-457.
2. Minns RA, **Goh D**, Pye SD, Steers AJW. A Volume - Blood Flow Velocity (VFR) relationship derived from CSF compartment challenge as an index of progression of infantile hydrocephalus. In: Matsumoto S, Tamaki N (eds) *Hydrocephalus: Pathogenesis and Treatment*. Springer Verlag Tokyo, Berlin, Heidelberg 1991; 270-278.
3. **Goh D**, Minns RA, Pye SD. Transcranial Doppler (TCD) Ultrasound as a non-invasive means of monitoring cerebrohaemodynamic change in hydrocephalus. *European Journal of Pediatric Surgery* 1991; 1, Suppl. I: 14-17.
4. **Goh D**, Minns RA, Hendry GMA, Thambyayah M, Steers AJW. Cerebrovascular resistive index assessed by Duplex Doppler sonography and its relationship to intracranial pressure in infantile hydrocephalus. *Pediatric Radiology* 1992; 22: 246 - 250.
5. **Goh D**, Minns RA, Pye SD, Steers AJW. Cerebral Blood Flow Velocity response to intermittent intracranial pressure elevation during sleep in hydrocephalic children. *Developmental Medicine and Child Neurology* 1992; 34: 676-689.
6. **Goh D**, Minns RA. Cerebral blood flow velocity monitoring in pyogenic meningitis. *Archives of Disease in Childhood* 1993; 68: 11-119
7. **Goh D**, Minns RA. Intracranial pressure and cerebral arterial flow velocity indices in hydrocephalus: current review. *Child's Nervous System* (accepted for publication).

Cerebral blood flow velocity changes after ventricular taps and ventriculoperitoneal shunting

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Abstract. Transcranial Doppler ultrasonography (TCD) was performed on 14 patients with hydrocephalus (age range 1 day to 12 years old) before and after ventriculoperitoneal shunting. TCD was also performed with simultaneous intracranial pressure (ICP) measurements during ventricular taps through a reservoir in 7 patients. Measurements of the resistance index ($RI = (S - D)/S$, peak systolic (S), enddiastolic (D) and time-averaged mean flow velocities were made. After ventricular taps and ventriculoperitoneal shunting there was a significant decrease in RI in all patients. This was due to a greater increase in D compared to S, which suggests a decreased distal cerebrovascular resistance. There was a significant correlation between RI and ICP in the older infants and children and in individual neonates. Successful cerebrospinal fluid diversion reduces ICP and cerebrovascular resistance, thus improving cerebral perfusion. The RI is a reliable index for serial monitoring of cerebrohaemodynamic change in patients with hydrocephalus.

Key words: Hydrocephalus – Ventriculoperitoneal shunting – Transcranial Doppler ultrasonography – Resistance index

Childhood hydrocephalus of congenital and acquired aetiology is a significant problem with a worldwide mean incidence of 6.85 per 10 000 births [7]. Progressive ventricular dilation and raised intracranial pressure (ICP) cause diminished cerebral blood flow and oedema with subsequent further tissue destruction. However, early diversion of cerebrospinal fluid (CSF) in order to reduce ICP at a reversible stage is associated with a return to normal of the caliber form and course of the cerebral vasculature [25]. The majority of patients with shunted hydrocephalus, however, remain shunt dependent and are thus at risk of further ischaemic insult as gradual or abrupt deterioration of shunt function may occur. Moreover,

clinical signs and symptoms of raised ICP are highly variable and unreliable [13], and thus an easily applied means of monitoring cerebral perfusion compromise would be helpful.

Cerebral Doppler sonography as a non-invasive and easily repeatable means of assessing cerebrohaemodynamic change was initially only possible in young infants with an open anterior fontanel [3]. Transcranial Doppler sonography (TCD) techniques, first described by Aaslid et al. [1] using pulsed-wave Doppler through the relatively thin temporal squamous bone, allow us to measure cerebral blood flow velocity (CBFV) in the basal cerebral arteries in all age groups. From the CBFV waveforms, we made measurements of Pourcelot's resistance index (RI) [20], time-averaged mean flow velocity (MFV), peak systolic velocity (S) and end-diastolic velocity (D). The RI is a calculated ratio ($RI = (S - D)/S$) and the MFV is the time-averaged mean of the maximum velocity envelope. The RI minimizes the effect of a variable angle of insonation and Archer et al. [2] have demonstrated a significant correlation between RI and distal cerebrovascular resistance in neonates. Assuming a constant vessel diameter, change in MFV may provide an index of change in mean volume flow [4].

The aim of our study was to assess cerebrohaemodynamic change using TCD in a mixed group of children with hydrocephalus before and after ventriculoperitoneal shunting (VPS).

Materials and methods

Fourteen patients (8 males, 6 females), age range 1 day to 12 years, underwent TCD monitoring before and after insertion or revision of a VPS. Table 1 summarizes their medical diagnostic background. As normal ranges of RI differ widely, the patients were divided into two groups: group I were neonates ($n = 5$) and group II were between 7.5 months and 12 years ($n = 9$). RI decreases from a mean of 0.71 for term infants to 0.5 after the 1st year of life and remains relatively constant thereafter [6]. The underlying aetiology of hydrocephalus was meningocele ($n = 5$), posthaemorrhagic ($n = 3$), postinfective ($n = 1$), aqueduct

Table 1. Medical diagnostic background. VPS, Ventriculoperitoneal shunt: +, pre-existing shunt, -, no previous shunt

Patient no.	Sex	Age	Aetiology of hydrocephalus	VPS
<i>Group I (neonates)</i>				
1	F	4 weeks	Perinatal infection	-
2	M	1 day	Congenital X-linked	-
3	M	2 weeks	Meningomyelocele	-
4	M	1 day	Meningomyelocele	-
5	F	1 week	Prenatal haemorrhage	-
<i>Group II</i>				
6	F	10 months	Arachnoid cyst	-
7	M	5 months	Idiopathic	-
8	F	12 years	Cerebellar astrocytoma	-
9	M	6 years	Aqueduct stenosis	+
10	M	14 months	Posthaemorrhagic	-
11	F	4 years	Posthaemorrhagic	+
12	M	9 years	Meningomyelocele	+
13	F	11 years	Meningomyelocele	+
14	M	12 months	Meningomyelocele	+

Table 2. Intracranial pressure (ICP) and Doppler indices pre- and post-ventricular taps. RI, Resistance index; MFV, time-averaged mean flow velocity; S, peak systolic velocity; D, end-diastolic velocity; SD, Standard deviation; NS, not significant

	Pre-tap mean (SD)	Post-tap mean (SD)	P value
<i>Group I (neonates: 4 patients)</i>			
RI	0.77 (0.05)	0.69 (0.05)	<0.001
MFV (cm/s)	47.2 (8)	54.3 (8)	<0.001
S (cm/s)	85.0 (7)	90.0 (8)	<0.02
D (cm/s)	17.3 (4)	26.3 (5)	<0.01
ICP (mm Hg)	9.8 (2.7)	4.7 (1.5)	<0.001
<i>Group II (children: 3 patients)</i>			
RI	0.65 (0.05)	0.50 (0.03)	<0.03
MFV (cm/s)	59.7 (22)	66.9 (12)	NS
S (cm/s)	97.7 (30)	99.1 (23)	NS
D (cm/s)	35.0 (14)	44.9 (9)	NS
ICP (mm Hg)	16.0 (4)	5.7 (1.5)	NS

stenosis ($n=2$), arachnoid cyst ($n=1$), cerebellar astrocytoma ($n=1$), and idiopathic ($n=1$). Six patients in group II had pre-existing shunts.

The indications for insertion or revision of VPS were increased ventricular dilation on ultrasound or computed tomography (CT) scan and raised intraventricular pressure measured directly via a ventriculostomy reservoir where available. A separate frontal reservoir is usually inserted in most of our patients with hydrocephalus to allow access for ICP measurement and emergency CSF drainage as required [16].

Eight patients were shunted for the first time: five neonates (nos. 1–5) and three group II patients (nos. 6–9). In group I, one term neonate (no. 2) had gross congenital X-linked hydrocephalus with an occipitofrontal circumference of 49 cm at birth, two neonates (nos. 3 and 4) had increased ventricular dilation after primary closure of myelomeningocele, and two (nos. 1 and 5) had progressive ventricular dilation despite regular ventricular taps. In the group II patients, two infants aged 5 and 10 months (nos. 6 and 7) presented with clinical symptoms of raised ICP supported by ultrasound and CT scan evidence of significant ventricular dilation. One patient aged 12 years (no. 8) developed symptoms of raised ICP after surgical removal of a

cerebellar astrocytoma, which had bled on initial presentation. In the six previously shunted patients, three (nos. 9–11) presented with typical symptoms of raised ICP, i.e. headache and vomiting, one with a persistent pain at the back of his neck (no. 12), one with increased clumsiness and deterioration in academic performance (no. 13), and one was asymptomatic (no. 14) with increased head circumference and increased ventricular dilation on CT scan.

Doppler ultrasound signals were obtained using a 2 or 4 MHz pulsed-wave probe attached to a portable Doppler unit (Decoder, Doptek Ltd, Chichester, UK). The middle cerebral artery was chosen for its accessibility and reliability and was insonated through the temporal bone using the technique described by Aaslid [1]. The Decoder performs real-time spectral analysis on the ultrasound signal and displays a spectrogram with 64 grey levels in time increments of 5, 10, 20 or 40 ms. The Doppler high-pass filter level was always set at 100 Hz. Forward and reverse-flow Doppler signals were recorded on the two channels of a high-quality audio cassette deck (Yamaha KX500). A remote control box attached to the cassette deck allowed voice dubbing of patient and ICP information onto tape. The Doppler recordings were subsequently played back and analysed and values of RI, MFV, S and D were measured. Each calculated value was obtained from the mean of at least 5–10 consecutive stable waveforms of good quality. The outline of the maximum velocity envelope was traced by hand using a light pen and the Doppler indices were calculated by software in the Decoder. This method allows accurate measurements to be made; background noise in the spectrogram could be ignored, as could waveforms distorted by patient or probe movement.

Direct intraventricular pressure was measured in ten patients using a nondisplacement strain-gauge pressure transducer (Gaeitec Ltd) attached to a 25-gauge butterfly needle inserted percutaneously in a reservoir. The pressure transducer was calibrated against a sphygmomanometer before each procedure. If the opening ICP was raised, CSF was drained in incremental volumes until the ICP was within normal range for the patient's age [18]. Doppler signals were continuously recorded throughout the procedure and corresponding ICP measurements were noted. Linear regression of corresponding RI versus ICP was obtained and pre- and post-tap Doppler indices were compared using a paired *t*-test. TCD was also performed on the infants at the bedside while they were asleep or resting quietly. Where possible, this was done on several occasions both before and after shunting. The mean values of Doppler indices preoperatively were compared to mean values postoperatively in individual patients using a paired *t*-test. Significance was set at conventional levels, i.e. the 5% level.

Results

Pre- and post-ventricular tap

Preoperative ICP measurements were performed in ten patients and corresponding ICP and CBFV data pre- and post-CSF taps were available in seven patients. The mean (standard deviation) ICP preoperatively in the neonatal group was 11.6(6) mm Hg and 17.2(5) mm Hg in group II, i.e. above normal range for age in both groups [18]. Table 2 shows mean Doppler indices and ICP from paired measurements before and after CSF taps in group I and II patients. The standard error of the standard deviation for the RI, MFV, S and D was 1.162^{-03} , 0.17 cm/s, 0.22 cm/s and 0.13 cm/s, respectively. There was a significant change in ICP and all Doppler indices in the neonatal group. The decrease in RI was caused by a larger change in diastolic velocity than in systolic velocity. The increase in diastolic velocity and decrease in ICP

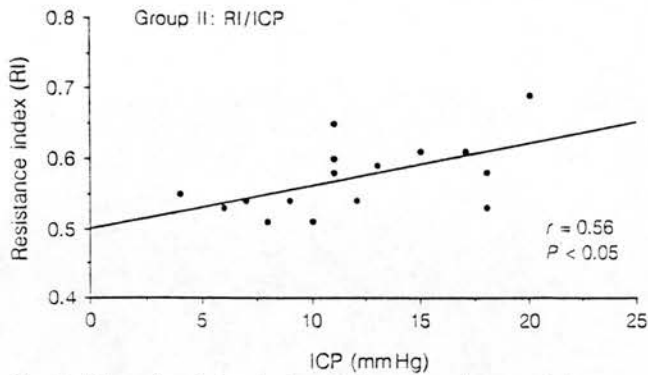


Fig. 1. Plot of resistive index (RI) against intracranial pressure (ICP) measurements (16 data sets) during ventricular taps in group II patients (children aged 5 months–12 years), which shows an overall significant positive correlation ($r=0.56$, $P<0.05$)

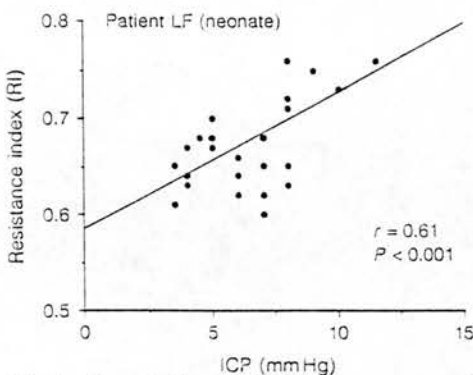


Fig. 2. Plot of RI against ICP measurements (31 data sets) during ventricular taps in a neonatal patient aged 4 weeks showing a significant positive correlation ($r=0.61$, $P<0.001$)

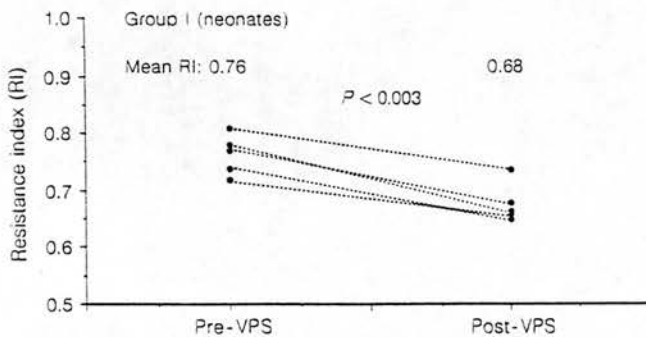


Fig. 3. Paired mean RI values in five group I patients (neonates) before and after ventriculoperitoneal shunting (VPS), which shows a significant decrease in RI post-VPS (paired t -test; $P<0.003$)

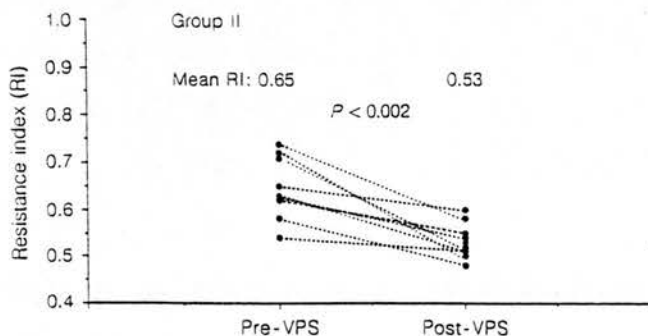


Fig. 4. Paired mean RI values in 9 group II patients (children aged 5 months–12 years) before and after VPS, which shows a significant decrease in RI post-VPS (paired t -test; $P<0.002$)

Table 3. Doppler indices pre- and post-VPS

	Pre-VPS mean (SD)	Post-VPS mean (SD)	P value
Group I (neonates: 5 patients)			
RI	0.76 (0.03)	0.68 (0.04)	<0.003
MFV (cm/s)	41.0 (11)	55.0 (10)	<0.003
S (cm/s)	75.8 (18)	89.0 (12)	<0.03
D (cm/s)	18.4 (5)	26.9 (6)	<0.004
Group II (9 patients)			
RI	0.65 (0.07)	0.53 (0.04)	<0.002
MFV (cm/s)	55.6 (13)	65.9 (12)	NS
S (cm/s)	97.8 (20)	97.1 (17)	NS
D (cm/s)	35.0 (10)	45.1 (8)	<0.02

after CSF drainage suggests that the decreased RI and increased MFV obtained reflects a reduced distal cerebrovascular resistance resulting in increased flow. In group II, there was a significant decrease in RI ($P<0.03$), but no significant increase in MFV post-tap.

There was an overall correlation ($r=0.56$, $P<0.05$) between RI and ICP in group II patients (Fig. 1). Overall correlation between RI and ICP was poor in the neonatal group, but in two neonates where there were sufficient data sets from repeated ventricular taps there was an improved correlation for each patient individually (Fig. 2; $r=0.61$ and 0.4 , $P<0.001$).

Pre- and post-VPS

Table 3 shows mean Doppler indices before and after successful VPS in all patients. RI decreased significantly in group I (Fig. 3, $P<0.003$) and group II (Fig. 4, $P<0.002$) patients after successful shunting. MFV increased in 10/14 patients, but again this was only statistically significant in the neonatal group. Diastolic velocity increased significantly and by a greater proportion compared to systolic velocity in both groups. ICP measurements were not performed after VPS when patients were clinically improved postoperatively, and early repeat cranial ultrasound scans showed no further ventricular dilation. Doppler indices before and after shunting were similar to values pre- and post-ventricular taps (Tables 2, 3). This suggests that successful CSF diversion reduces ICP and cerebrovascular resistance, thus improving cerebral perfusion.

Case illustrations

Case 1. Patient 2 had gross X-linked congenital hydrocephalus. Mean serial RI and MFV performed over the first 4 days of life prior to his first VPS and frontal reservoir insertion on day 5 was 0.73 and 38 cm/s. On the first postoperative day, RI had decreased to 0.65 and MFV was 37 cm/s. However, he developed ventriculitis postoperatively requiring removal of his VPS and he received intrathecal antibiotics through his reservoir for 2 weeks.

He had a replacement VPS performed and his postoperative course after this second VPS was uncomplicated. Mean serial RI and MFV during the period with ventriculitis between the first and second shunt was 0.69 and 35 cm/s and subsequently following the second shunt was 0.66 and 54 cm/s. Thus, the Doppler indices suggested consistently improved flow only after the second successful VPS, which was uncomplicated by postoperative ventriculitis. His cerebral ultrasound scans after the second VPS showed a marked decrease in ventricular size.

Case 2. Patient 5 had hydrocephalus diagnosed on antenatal scan just prior to delivery, thought possibly to be due to a prenatal intraventricular haemorrhage, as postnatal scans showed evidence of thrombus in the posterior lateral ventricle. Ventricular dilation progressed despite repeated ventricular taps through a frontal reservoir (ICP between 7 and 10 mm Hg) and the first VPS was performed at 5 weeks. Mean RI and MFV before first VPS were 0.78 and 46 cm/s. However, there was no significant clinical improvement or change in ventricular size and head circumference measurement postoperatively. Repeat ICP measurement from ventricular taps after the first VPS showed that ICP remained elevated between 8 and 9 mm Hg. A second VPS was performed 7 days later and the first VPS was found to be proximally blocked by cellular debris. Mean RI and MFV between the 1st and 2nd VPS was 0.76 and 54 cm/s and after the 2nd successful VPS was 0.66 and 64 cm/s. Serial Doppler indices in this patient again illustrated improvement in flow only after the second successful VPS and gave an additional indication of inadequate shunt function after the first unsuccessful VPS.

Case 3. Patient 6 was referred at the age of 10 months with a head circumference over the 97th percentile, which had increased from the 50th percentile at 6 months of age. Her anterior fontanel was tense on palpation. Cerebral sonography and CT scan showed dilated lateral ventricles with a suprasellar arachnoid cyst. The initial RI was 0.72. Operative drainage of the cyst and insertion of a frontal reservoir was performed with an initial clinical improvement and slight decrease in ventricular size and mean RI was then 0.64. However, within 12 days she was again more irritable with a tense fontanel and raised ICP (15 mm Hg). A ventriculoperitoneal shunt was then performed with marked subsequent improvement and mean RI after VPS further decreased to 0.5.

Discussion

There are a number of techniques for the measurement of cerebral blood flow in children [14]. Of these, techniques using radioisotopes, particularly xenon 133, are considered to be among the most reliable and reproducible, but the risk from repeated exposure, particularly to young infants, is unknown and this limits its suitability for monitoring purposes. New techniques such as proton emission tomography and near infrared spectroscopy are not

yet widely available. Transcranial Doppler ultrasound is non-invasive, causes negligible discomfort and can readily be repeated at the bedside; thus, its advantages for monitoring cerebrohaemodynamic change are obvious. However, careful interpretation of CBFV changes are required, as changes in flow velocity do not indicate similar changes in volume flow if the vessel calibre alters. For example, after subarachnoid haemorrhage, increased velocity has been reported to reflect vasospasm [9]. Finn et al. [8] have demonstrated that a significant insonation angle error may occur when intracranial anatomy is distorted, as may be the case in hydrocephalus, and they suggest that RI may be a more reliable haemodynamic parameter compared to absolute velocity measurements.

The cerebral arterial waveform may be altered by factors other than the cerebrovascular resistance which also influence its flow characteristics, e.g. the presence of a patent ductus [19], raised intrathoracic pressure in pneumothorax [11] or polycythaemia [21]. These factors pose a greater clinical problem in preterm neonatal patients and may affect interpretation of observed flow changes. Apart from their hydrocephalus and its associated complication (ventriculitis), all our patients were in a stable clinical condition with no evidence of cardiovascular or respiratory instability. There was no significant alteration of haematocrit during their study period. All group I patients were of term gestation when studied.

An increased RI has been commonly reported in hydrocephalus [10, 17, 22, 24]. An explanation that the increased RI is due to altered cerebrovascular compliance rather than distal resistance has been suggested by Van Bel et al. [24], as they found that systolic rather than diastolic velocity was significantly altered. However, measurements of ICP were not obtained in their patients, which is a critical factor in the intracranial dynamics of hydrocephalus and has a major effect on cerebral perfusion. Van Bel et al. [24] assumed that ICP was likely to be normal in their patients because they were studied at an early stage of posthaemorrhagic hydrocephalus (3–33 days). However, Kaiser and Whitelaw [12] have shown that raised ICP was associated with progressive increase in ventricular dilation. Over many years of obtaining direct intraventricular pressure measurements through reservoirs in our clinical management of hydrocephalus, in our experience progressive hydrocephalus with intracranial hypertension can certainly occur early within the first 2 weeks of life. Lui et al. [17] reported that the RI showed a consistent trend of increase with ventricular dilation, although a maximal RI value of 1.0 was also seen in two patients whose ventricular dilation was graded of only moderate severity. They assumed that raised ICP played a significant role in these cases, although ICP was also not measured in this study.

Seibert et al. [22] have shown a significant correlation between cerebral perfusion pressure and RI in an experimental canine model. They have also reported that a raised RI in conjunction with clinical observations was helpful in predicting the need for VPS in 46 infants with ventriculomegaly [6]. An increased RI has also been demonstrated in adult patients with raised ICP due to heterogeneous severe cerebral diseases [15].

Our results show a consistent decrease in RI in all patients after successful VPS, supporting the observations made by Seibert et al. [6]. The range of RI values we have observed in our neonatal and older children before and after treatment are similar to the values they reported, thus confirming the RI as a reliable and reproducible index in assessing cerebrohaemodynamic change in hydrocephalus. The decrease in RI after ventricular taps and shunting was due to a greater significant increase in diastolic rather than systolic velocity, suggesting a decrease in cerebrovascular resistance after CSF drainage or diversion. This paper reports the only data we are aware of which show a correlation between directly measured ICP and RI in older children and in individual neonatal patients. This further supports the use of RI as a reliable index for monitoring perfusion change in individual patients.

The overall poor correlation between RI and ICP in the neonatal group may be due to variably altered intracranial compliance states in individual neonates where the cranial sutures are still unfused and intracranial biomechanical characteristics are non-uniformly affected by the early progressive hydrocephalic process, resulting in enhanced volume storage capacity [23]. In comparison, in older infants and children, especially those who have been shunted, the cranial sutures are mainly fused and intracranial pressure dynamics may be more uniform within a defined and limited intracranial vault.

The MFV was generally increased after shunting, but was a less reliable index than the RI. It was only consistently increased in the neonatal group, and this may have been due to the normal rapid increase in CBFV during the 1st month of life [5]. The error due to a variable insonation angle may be significant when serial measurements are compared, as it is of course difficult to be certain of always placing the probe at precisely the same position on different days and distorted intracranial anatomy due to ventricular distension in hydrocephalus may compound this error. However, an increased MFV when seen in conjunction with a decreased RI suggests an increase in cerebral blood flow. Although normal ranges of MFV have been published [5], the range is fairly wide and, without knowing the true cross-sectional area of cerebral blood vessels in individual patients, MFV cannot be reliably used for interindividual comparison of true cerebral blood flow. The more appropriate use of CBFV indices is in serial studies of individual patients, although RI values clearly outside the normal range, especially if there is no diastolic flow, reliably indicate impaired cerebral perfusion, assuming no other significant haemodynamic factors are present such as a patent ductus arteriosus.

Conclusion

In summary, we have shown a significant change in CBFV with a decreased RI and increased MFV, suggesting that improvement in cerebral perfusion occurs after successful CSF diversion by VPS. The RI is a more reliable index for serial monitoring of cerebral perfusion

in patients with hydrocephalus. Transcranial Doppler sonography is thus a reliable and readily available non-invasive bedside technique of monitoring cerebrohaemodynamic change and thus very helpful in the initial evaluation and further management of childhood hydrocephalus. Further clinical studies are, however, required to evaluate accurate indications for shunting.

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Transcranial Doppler (TCD) Ultrasound as a Noninvasive Means of Monitoring Cerebrohaemodynamic Change in Hydrocephalus

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Summary

Cerebral blood flow velocity (CBFV) measurements by Transcranial Doppler (TCD) ultrasound were performed on 27 patients with hydrocephalus (Group I: neonates, Group II: children). Simultaneous measurements of direct ICP and CBFV were performed during ventricular taps in 16 patients. There was a significant correlation between ICP and Resistance Index (RI = peak systolic-end diastolic/peak systolic velocity) overall in Group II patients ($p < 0.02$) and in individual neonatal patients ($p < 0.001$). After ventricular taps and ventriculo-peritoneal shunting (17 patients) there was a consistent significant decrease in RI due to increased end diastolic velocity in all patients ($p < 0.001$). This suggests the RI is a reliable index of cerebrovascular resistance for serial monitoring in individual patients. There was an exponential pattern of decay in RI with CSF volume depletion (volume-flow velocity response) in 50/56 taps which allows calculation of a volume-buffering reserve before perfusion change occurred. Simultaneous ICP/CBFV monitoring during sleep may help to identify patients who are unable to compensate haemodynamically during episodic increase in ICP and are a greater risk of ischaemic insult. TCD is a useful noninvasive technique of monitoring cerebrohaemodynamic change for initial assessment and further management of children with hydrocephalus.

Key words

Transcranial Doppler ultrasound - Hydrocephalus - Resistance Index

Introduction

Progressive hydrocephalus causes secondary damage due to ischaemic effects from raised intracranial pressure or brain shifts. Spontaneous arrest can occur in some patients before significant ischaemic damage occurs and shunting procedures could then be avoided. Complications of shunting such as infection, blockage and overdrainage remain considerable problems. Repeated assessment of cerebral perfusion is thus important for optimal management from the initial evaluation at diagnosis, observation for progression or arrest through to monitoring for long-term shunt complications. Most currently

widely available techniques of monitoring cerebral perfusion which are applicable to all age groups usually involve exposure to radioactive isotopes, eg. Xenon 133, and thus repeated exposure for monitoring purposes is not justifiable particularly in young children. Transcranial Doppler (TCD) ultrasound techniques (1) provide a noninvasive means of measuring cerebral blood flow velocity (CBFV) in the basal cerebral arteries. We have assessed the use of TCD for monitoring cerebrohaemodynamic changes in children with hydrocephalus at initial evaluation as well as in those who have been shunted. This paper will report on changes in Doppler CBFV indices in relation to CSF volume manipulation and to spontaneous episodic ICP elevations associated with cerebral blood volume changes occurring in sleep.

The Pourcelot Resistance Index (10), RI = (systolic-diastolic)/systolic velocity has been applied as an index of distal cerebrovascular resistance if RI increases due to a decrease in diastolic velocity. Archer et al (2) demonstrated a decreased RI with hypercapnia-induced increased cerebral blood flow in healthy neonates. Assuming a constant vessel diameter, change in mean flow velocity (MFV) may provide an index of change in mean volume flow (4).

Materials and methods

Patients

TCD examinations were performed on 27 patients: 11 were neonatal patients (Group I) and 16 patients were between 1 to 14.3 years of age (Group II). Eleven of the Group II patients had existing ventriculo-peritoneal shunts at the time of assessment. The patients were divided into two groups because values of the normal range of RI in children differ from neonatal patients (5).

(1) Doppler changes were assessed in relation to CSF volume manipulation:

- Ventricular taps were performed in 16 patients (Group I: 10; Group II: 6).
- Ventriculo-peritoneal shunting/revision (VPS) procedures were performed in 17 patients (Groups I: 8; Group II: 9).

(2) Doppler changes were assessed in relation to spontaneous ICP increases due to cerebral blood volume changes in sleep: Eight sleep recordings were performed on 7 patients (Group II).

Ventricular taps were performed when there was a progressive increase in ventricular dilatation or when clinical signs and symptoms of raised ICP were present. Operative intervention was indicated when raised ICP levels confirmed blocked or inadequate shunt

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function and in new patients, when there was no evidence of spontaneous arrest occurring after repeated taps. Prolonged sleep monitoring was carried out in patients with intermittent or chronic symptoms while ICP levels from single, brief measurements were normal or equivocal.

Methods

ICP was directly measured through a 23-gauge butterfly needle inserted percutaneously in a frontal ventriculostomy reservoir using a nondisplacement strain gauge pressure transducer (Gaeltec Ltd) and simultaneously charted by a pen recorder. A separate reservoir was usually placed in all our patients to allow access for repeated ICP measurement and CSF drainage as required (8). If ICP levels were elevated for age, CSF was drained in 1 ml increments through a three-way tap arrangement until ICP levels were within normal range for age.

CBFV was measured from the middle cerebral artery using pulsed-wave Doppler from a portable unit (Decoder, Doptek Ltd) with a 2 or 4 MHz probe. Doppler signals were recorded on a cassette deck while a remote control unit allowed voice-dubbing of ICP and CSF volume information onto tape. Doppler signals were subsequently played back and values of the RI, time-averaged MFV, peak-systolic (S) and end-diastolic (D) velocities were obtained by tracing the outline of the maximum velocity envelope using a light pen. Each calculated mean value represents the mean of ~ 10 stable waveforms of good quality.

1 a) CBFV measurements were made continuously throughout a ventricular tap with the corresponding ICP levels during the tap noted. Linear-regression of ICP versus RI was obtained and pre- and post-tap ICP and Doppler indices were compared using paired t-test.

1 b) TCD examinations were also performed in quiet bedside conditions where possible on several occasions before and after shunting. The mean values of Doppler indices pre-operatively were compared to mean values post-operatively in individual patients by paired t-test.

2) For prolonged sleep recordings, ICP was continuously charted and CBFV measurements were made at 10–15 minute intervals during stable ICP states and more frequently during changing ICP states with voice recording of simultaneous ICP information. CBFV measurements were made from a constant position and depth once the optimal signals were identified at the beginning of each recording to minimise the error due to a variable angle of insonation.

Results

Relationship between RI and ICP

Data were available from 50 taps in Group I and 3 taps in Group II patients. Group I: There was a poor overall correlation for the whole group but in 4 neonatal patients with sufficient repeated measurements there was a significant positive correlation between RI and ICP individually ($p < 0.001$, range of correlation, $r = +0.61$ to $+0.87$).

Group II: There was a significant overall correlation between RI and ICP ($p < 0.02$, $r = +0.70$).

CBFV indices before and after CSF drainage by ventricular taps

Mean (\pm standard deviation) values of ICP and Doppler indices before and after taps in Group I and II patients are shown in Table 1. ICP decreased significantly ($p < 0.01$) after CSF drainage. There was a highly significant decrease in RI ($p < 0.001$) in both groups after CSF volume depletion which was due to a significant

Table 1 Intracranial pressure (ICP) and Doppler indices pre- and post-ventricular taps.

	Pre-tap mean (sd)	Post-tap mean (sd)	p value
Group I (Neonates: 10 patients)			
RI	0.78 (.05)	0.68 (.06)	<.001
MFV (cm/sec)	40.7 (12)	48.2 (13)	<.001
S (cm/sec)	74.9 (18)	79.0 (19)	<.01
D (cm/sec)	15.8 (6)	24.6 (8)	<.001
ICP (mm Hg)	11.1 (3.5)	4.9 (1.3)	<.001
Group II (Children: 6 patients)			
RI	0.61 (.05)	0.51 (.03)	<.001
MFV (cm/sec)	59.7 (19)	71.5 (19)	ns
S (cm/sec)	95.8 (34)	103.8 (33)	ns
D (cm/sec)	36.9 (13)	49.1 (15)	<.03
ICP (mm Hg)	15.5 (3.5)	6.5 (2.3)	<.01

RI = Resistance Index, MFV = time-averaged mean flow velocity, S = peak systolic velocity, D = end diastolic velocity, sd = standard deviation, ns = not significant

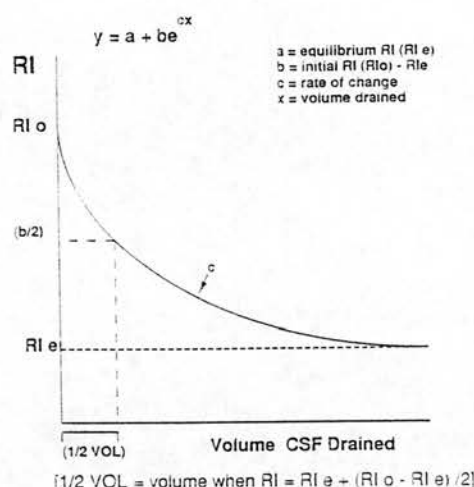


Fig. 1 shows a predicted exponential curve fit, $y = a - be^{-cx}$ for serial observed RI (Resistance Index) decay with volume depletion during CSF taps. Half-volume = $-0.7/c$, i.e. the volume drained when $1/2$ change in RI i.e. $(RI_o - RI_e)/2$ has occurred.

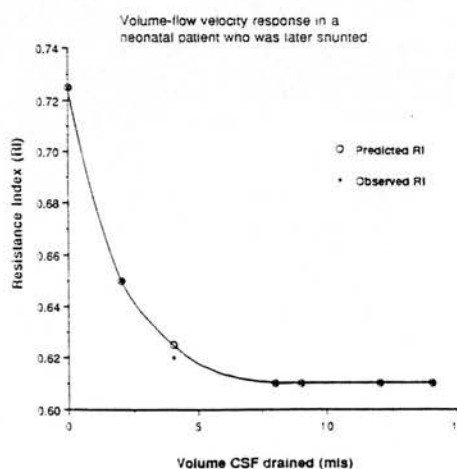


Fig. 2 Plot of predicted RI (open circles) and observed RI (closed squares) against CSF volume drained in a neonatal patient requiring shunting which illustrates a rapid exponential decay in RI.

Table 2 Doppler indices pre- and post-ventriculoperitoneal shunting/revision (VPS).

	Pre-VPS mean (sd)	Post-VPS mean (sd)	p value
Group I (Neonates: 8)			
RI	0.76 (.04)	0.68 (.05)	<.001
MFV (cm/sec)	36.6 (11)	50.3 (12)	<.001
S (cm/sec)	68.6 (19)	81.1 (19)	<.01
D (cm/sec)	16.7 (5.5)	26.4 (7.4)	<.001
Group II (Children: 9)			
RI	0.65 (.07)	0.53 (.04)	<.001
MFV (cm/sec)	55.6 (13)	65.9 (12)	ns
S (cm/sec)	97.8 (20)	97.1 (17)	ns
D (cm/sec)	35.0 (9.5)	45.1 (8)	<.02

RI - Resistance Index, MFV - mean flow velocity, S - peak systolic velocity, D - end diastolic velocity, sd - standard deviation, ns - not significant

increase in end-diastolic velocity (D). Increase in peak-systolic velocity (S) and MFV was only significant in Group I patients.

CBFV indices before and after ventriculo-peritoneal shunting or revision

Mean (\pm sd) values of Doppler indices before and after shunting procedures are shown in Table 2. Similarly, there was a highly significant decrease in RI ($p < 0.001$) after successful CSF diversion in both groups which was again due to a significant increase in D. Increase in S and MFV after shunting was only significant in Group I.

Exponential pattern of decrease in RI against volume of CSF drained

As there was a significant linear correlation between RI/ICP, theoretically there could be also an exponential relationship between RI and CSF volume similar to the ICP/volume relationship. Serial RI values plotted against CSF volume drained for individual taps were

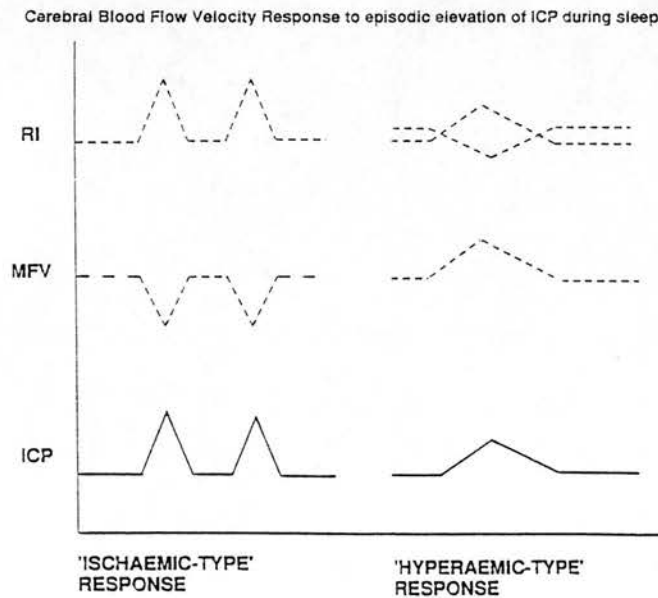


Fig. 3 Schematic diagram illustrating the "ischaemic-type" cerebral blood flow velocity response with simultaneous decreased mean flow velocity (MFV) and increased resistance index (RI) to episodic elevation in ICP during sleep. In the "hyperaemic-type" response MFV increased when ICP increased while RI change was variable (increased or decreased).

then fitted to an exponential equation, $y = a - be^{-cx}$ as shown in Figure 1 where RI₀ (initial RI) = $a+b$; $a = RI_e$ (equilibrium RI); $b = \text{change in RI}$ (RI₀ - RI_e); $c = \text{rate of change}$. 50 of the 56 ventricular taps fitted this exponential pattern and thus allowed calculation of a "half-volume" i.e. volume of CSF drained when half the change in RI ($b/2$) had occurred. Figure 2 illustrates the exponential decay in observed and predicted RI values during one of these taps. Calculation of the "half-volumes" could theoretically provide an estimate of residual volume buffering capacity before significant perfusion change occurs in each individual patient at the time of assessment. Repeated studies then may indicate if this volume-buffering capacity is increasing or decreasing in each patient. The mean (standard deviation) "half-volume" was 2.45 (2.8) mls in 8 neonates who required shunting, 2.13 (1.0) mls in 4 children with blocked shunts in contrast to 11.9 mls in one child who had dilated ventricles which remained stable (i.e. arrested) without shunting.

CBFV change in relation to ICP and cerebral blood volume changes in sleep

In 4 sleep studies there was an "ischaemic-type" CBFV response where increase in ICP was associated with an overall progressive decrease in MFV ($r = -0.44$, $p < 0.001$) and increase in RI ($r = +0.64$, $p < 0.001$). Three of the patients had slit ventricles on CT scan and plateau/A and B ICP waves were seen in two studies. In 4 studies there was a "hyperaemic-type" CBFV response where MFV increased with increasing ICP ($r = +0.65$, $p < 0.001$). Change in RI with ICP increase was variable in this group. Fig. 3 shows a schematic illustration of MFV and RI change in relation to ICP change during the "ischaemic" and "hyperaemic-type" CBFV responses. One patient with slit ventricles and overdrainage changed from an "ischaemic-type" response to a "hyperaemic-type" response after a skull morcellation procedure to enhance intracranial volume.

Discussion

Doppler cerebral blood flow velocity measurements as a noninvasive means of monitoring cerebrohaemodynamic trends has been widely investigated, particularly in premature infants, since Bada et al (3) first reported a raised RI associated with raised ICP after intraventricular haemorrhage. However the interpretation of change in Doppler indices remains debatable as other factors apart from cerebrovascular resistance and intracranial dynamics are also known to influence the cerebral arterial velocity waveform. The angle of insonation can vary considerably especially when the intracranial anatomy is distorted by ventricular distension in patients with hydrocephalus (7). Thus the RI, as a ratio, will minimise the effect of a variable angle of insonation in comparison to absolute velocity measurements and is likely to be a more reliable index for serial measurements. We have shown that the RI correlates reliably with ICP in individual neonatal patients and overall for older children with hydrocephalus. Overall correlation for neonatal patients may be less reliable because the unfused cranial sutures allow a highly variable degree of volume and ICP compensation in individual patients at varying stages of the hydrocephalic process and the normal range of ICP is a fairly narrow band in neonates. In contrast, the intracranial dynamics in older children with fused cranial vaults would be expected to be more uniform.

Our results support the RI as a reliable index of cerebrovascular resistance as we have also shown that after drainage of CSF and ICP is reduced, the resulting decrease in RI was due mainly to an increase in diastolic flow. It is highly unlikely that vasoconstriction of the middle cerebral artery would

be a cause for the observed general increase in absolute velocity measurements after CSF taps. Although we would not expect significant alteration of vessel calibre in a major artery to occur after CSF drainage, an increase rather than decrease would be more likely with reduction of ICP and increased transmural pressure. Alteration in vessel calibre would also be expected to uniformly affect change in MFV, S and D but our results have consistently shown that *after CSF volume depletion through taps or shunting* only RI and D were significantly altered. True levels of cerebral blood flow cannot be inferred from Doppler MFV values and interindividual comparisons are unreliable without knowledge of individual cerebral arterial cross-sectional areas. However our results show that the RI is a reliable index for serial monitoring of cerebrohaemodynamic trends in individual patients. This is of use practically when direct invasive measurement of ICP is not indicated or unavailable, eg. to confirm adequate shunt function postoperatively without causing a risk of infection through reservoir puncture, or when a separate reservoir is not present or not functioning. Noninvasive transfontanometric measurements of ICP are of course only applicable to young infants who still have adequately wide open fontanelles and shunted infants and children later presenting with complications such as overdrainage or shunt blockage cannot be assessed by these techniques.

Single measurements of ICP or cerebral perfusion are of limited use in assessment of volume-buffering or perfusion reserve in patients with hydrocephalus. Dynamic tests of intracranial compliance such as the pressure-volume index and estimation of CSF outflow resistance as described by Marmarou and colleagues (9) have been used in selection of patients for shunt operations. Improvement in cerebral perfusion is assumed from subsequent reduction in ICP. The *exponential relationship* we have shown *between RI and CSF volume depletion* suggests that this model may be very useful for directly assessing cerebral perfusion response to volume manipulation. It may be possible to estimate volume-buffering reserve before perfusion compromise occurs and thus serial measurements may allow us to predict if progression or arrest is occurring. Our study numbers are small and thus we are not able yet to define critical "half-volumes" for neonatal and older patients who may require shunting or revision. However we suggest that this may be useful for more reliable prediction of those who will benefit from shunting and further work on more patients is required.

Spontaneous episodic elevations in ICP are known to occur in association with increased *cerebral blood flow and volume changes during REM sleep* (6). Patients with reduced compliance are unable to compensate adequately for the increased cerebral blood volume thus producing significant ICP increase in the form of A and B waves. Our results from simultaneous monitoring of ICP and CBFV change during sleep suggest that the patients with an "ischaemic-type" response have limited cerebrovascular reserve and are unable to haemodynamically compensate adequately during the episodes of raised ICP. They would thus be at greater risk of ischaemic insult when ICP is elevated. In contrast, patients who showed a "hyperaemic-type" response may have sufficient cerebrovascular reserve and be able

to haemodynamically compensate through further pial arterial dilatation to maintain adequate cerebral perfusion during moderate increase in ICP. Although the RI is more reliable for serial monitoring, in our sleep studies change in MFV should provide a reliable index of blood flow changes in each study as the Doppler measurements were made from a constant position and depth after identification of the optimal signals at the beginning of each study. Our results suggest that simultaneous monitoring of ICP and CBFV changes during sleep may help to detect the patients with apparently "compensated" hydrocephalus but limited cerebrohaemodynamic reserve who are at risk of ischaemic insult during episodic elevation in ICP.

In conclusion, TCD is a portable, noninvasive and easily repeatable bedside technique of monitoring cerebrohaemodynamic trends and thus is ideally suited for monitoring infants and children with hydrocephalus. We have illustrated its role in various stages of management of hydrocephalus and although in our practice, the direct measurement of ICP when possible remains an important part of assessment, the combined use of TCD monitoring has provided additional valuable information on intracranial dynamics and perfusion.

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Cerebral blood flow velocity monitoring in pyogenic meningitis

Dayeel Goh, Robert A Minns

Abstract

Transcranial Doppler ultrasound monitoring of cerebral blood flow velocity (CBFV) was performed on 17 children (age range 8 days to 6 years) with pyogenic meningitis. Serial measurements of the peak systolic, end diastolic, mean flow velocity, and resistance index (equal to peak systolic velocity minus end diastolic velocity divided by peak systolic velocity) were obtained over the period of their hospital admission. In all 16 survivors there was a significant decrease in the final resistance index compared with the initial resistance index due to a significant increase in the end diastolic velocity. There was a significant increase in the final mean flow velocity. In four patients the decrease in intracranial pressure and increase in cerebral perfusion pressure after mannitol infusions was accompanied by a corresponding decrease in resistance index and increase in mean flow velocity. A pressure passive CBFV response with a significant linear correlation for resistance index/mean arterial pressure may suggest a loss of cerebrovascular autoregulation. These results suggest that in the early phase increased cerebrovascular resistance may contribute to a relative impairment of cerebral perfusion. Non-invasive monitoring by transcranial Doppler ultrasound may be helpful for early detection of deterioration in cerebral haemodynamic trends.

(Arch Dis Child 1993;68:111-9)

Bacterial meningitis is one of the most serious diseases in early childhood with a reported overall mortality rate of 8.6% in the first year of life.¹ Although mortality rates have improved, there is still a considerable long term morbidity ranging from 10 to 15%.² Impaired cerebral perfusion resulting from a variety of factors plays an important part in the pathogenesis of cerebral injury in meningitis.³ A minimum cerebral perfusion pressure of 30 mmHg was found to be an important factor for survival in children who were comatose from severe central nervous system infection.^{4,5} Minns *et al* have reported increased cerebrospinal fluid pressure to be a common accompaniment of pyogenic meningitis.⁶ Increased intracranial pressure is likely to be an early feature in the pathophysiology of pyogenic meningitis^{3,5} and contributes to reduced cerebral perfusion pressure. Cerebral infarction and oedema, shown by computed tomography, were reported to be predictive of a poor outcome whereas enlarged ventricular and subarachnoid spaces and subdural effusions

were of no predictive value.⁷ Monitoring cerebrohaemodynamic changes may be important for early detection of cerebral perfusion compromise with the aim of preventing further cerebral insult.

Although there are a number of techniques available to measure cerebral perfusion, most are either invasive or not practical for continuous monitoring purposes. Transcranial Doppler ultrasound provides a non-invasive means of measuring cerebral blood flow velocity (CBFV) in the basal cerebral arteries.⁸ Analysis of changes in the CBFV waveforms has been widely reported in a number of clinical disorders such as hydrocephalus,⁹⁻¹¹ subarachnoid haemorrhage,¹² brain stem death,¹³ and neonatal cerebrohaemodynamics and in normal neonates.¹⁴ There have, however, only been two published reports on CBFV changes in childhood meningitis.^{15,16} McMenamin and Volpe reported a depressed mean flow velocity associated with increased intracranial pressure in four older infants (mean age 5.75 months) during the initial phase of the illness.¹⁵ In contrast, decreased mean flow velocity and increased intracranial pressure were not present in their four newborn patients. Bode and Harders, however, reported a marked (up to fivefold) and persistent increased mean flow velocity in the middle cerebral artery in three of their 14 patients with meningitis, which was attributed to significant vessel narrowing causing secondary ischaemic damage as these patients had a poor outcome.¹⁶ The moderately increased flow velocities in the 11 patients with a favourable outcome was ascribed to increased cerebral blood flow.

With increased distal resistance to flow, the Pourcelot resistance index increases steadily as the diastolic velocity decreases,¹⁷ for example, with steady increase in intracranial pressure in hydrocephalic children,¹¹ and with intracranial circulatory arrest when intracranial pressure approaches the systemic diastolic blood pressure, diastolic CBFV approaches zero.¹³ The resistance index was also significantly related to increased intracranial pressure in comatose adults¹⁸ and to reduced cerebral perfusion pressure due to increasing intracranial pressure in an experimental animal model.¹⁹ Changes in mean flow velocity may, however, be due to changes in mean volume flow²⁰ or due to alteration in the calibre of the insonated vessel as a result of vasospasm or stenosis. After a subarachnoid haemorrhage, a mean flow velocity <120 cm/s is suggestive of significant vasospasm accompanied by low volume flow.¹²

With the obvious practical advantages of

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transcranial Doppler ultrasound as an easily repeatable, safe technique, it is now becoming widely applied in bedside monitoring of cerebrohaemodynamic trends in neurointensive care management.²¹ Careful interpretation of changes in CBFV indices is required in various clinical situations, however.¹⁴ We describe our experience in using transcranial Doppler ultrasound as a non-invasive method of monitoring cerebrohaemodynamic changes in 17 children who were admitted with pyogenic meningitis.

Patients and methods

Seventeen patients (nine boys, eight girls) who were admitted with a diagnosis of pyogenic meningitis were monitored during the course of their admission by transcranial Doppler ultrasound. Table 1 summarises their clinical details. Their age range was from 8 days to 6 years; four patients were less than 3 months old (group I) and 13 patients were between 6 months and 6 years old (group II). The patients were allocated to two groups as the normal range of CBFV data is age dependent¹⁰⁻²² (table 2) and also to allow comparison with previously published data.¹⁵ Initial transcranial Doppler ultrasound examination was performed within the first two days after admission and then repeated at intervals during their admission, more often during the early days. Three patients were transferred from other hospitals after not improving satisfactorily. Three patients required ventilatory and intensive care support on admission. In four patients CBFV recordings with simultaneous intracranial pressure and cerebral perfusion pressure measurements before and after mannitol infusions were obtained. Cerebral imaging by transfontanelle sonography was performed in 10 infants and computed tomography scans in three children with clinical signs of increased intracranial pressure or with persistent pyrexia and irritability.

The organisms isolated from the cerebrospinal fluid were group B haemolytic streptococci (two), *Escherichia coli* (one), *Neisseria meningitidis* (five), *Haemophilus influenzae* type b (six),

Streptococcus pneumoniae (one), and *Salmonella enteritidis* (one). In one patient (No 12) who had received antibiotics before admission and before cerebrospinal fluid was obtained (lumbar puncture deferred until the second day), no specific bacterial or viral agent was isolated and counter current immunoelectrophoresis antigen screening was also negative. The cerebrospinal fluid leucocyte count was markedly increased ($4.5 \times 10^9/l$; 84% neutrophils) and he showed a rapid clinical response to antibiotic treatment, thus suggesting most likely a bacterial aetiology. Only one patient (patient No 1, a 2 week old neonate with group B haemolytic streptococcal infection) died during this study.

CBFV MEASUREMENTS

CBFV was measured in the middle cerebral artery using a 2 or 4 MHz pulsed wave probe attached to a portable Doppler unit (Decoder, Doptek Ltd). The middle cerebral artery is a major branch of the carotid system and is most easily and reliably insonated at a minimum angle from the temporal position (at a depth ranging from 2.5 to 5 cm in our patients) using the technique described by Aaslid *et al.*⁸ The

Table 2 Normal ranges for resistance index and mean flow velocity

Age	Resistance index	Mean flow velocity (cm/s)
Bode and Wais ²²		
0-90 days	0.62-0.80	10-62
3-11.9 months	0.58-0.62	46-102
1-2.9 years	0.40-0.59	65-105
3-5.9 years	0.54 (0.4)-0.58 (0.62)	74-114
6-9.9 years	0.46-0.54	79-115
10-18 years	0.53-0.54	59-103
Chaddock and Seibert ¹⁰		
Term infants (>34 weeks' gestation): 0.71 (0.07)†		
27 children (18 months-16 years): 0.50 (0.15)†		
Goh and Minns (unpublished data)		
11 children (21-112 months): 0.45-0.61‡		

*Calculated normal ranges (mean (2SD)) from 112 healthy children (aged 1 day-18 years)

†Mean (SD) resistance index values.

‡Normal range of resistance index values.

Table 1 Clinical details of patients

Patient No	Age	Sex	Cerebrospinal fluid organism	Diagnostic cerebrospinal fluid		Glucose (mmol/l)	Radiological findings	Outcome at discharge
				Leucocytes ($\times 10^9/l$)	Protein (g/l)			
1	2 weeks	F	Group B streptococcus	0.5	3.9	None	Ultrasound: oedema, focal echogenicity	Died
2	8 days	M	<i>Escherichia coli</i>	10.4	4.18	2.3	Ultrasound: normal	Normal
3	13 days	F	Group B streptococcus	0.6	Blood	Stained	Ultrasound: normal	Normal
4	11 weeks	F	<i>Haemophilus influenzae</i>	1.4	0.97	<0.5	Ultrasound: bilateral subdural effusions	Normal
5	9 months	M	<i>Neisseria meningitidis</i>	7.1	1.38	<0.3	—	Normal
6	8 months	M	<i>Haemophilus influenzae</i>	4.9	0.92	<0.5	Ultrasound: bilateral subdural effusions	Normal
7	8 months	F	<i>Haemophilus influenzae</i>	1.9	0.54	<3.5	—	Normal
8	11 months	M	<i>Neisseria meningitidis</i>	20.8	2.92	<0.5	—	Normal
9	26 months	M	<i>Haemophilus influenzae</i>	0.7	1.28	<0.9	—	Normal
10	8 months	F	<i>Neisseria meningitidis</i>	6.7	1.21	<1.6	Ultrasound: normal	Normal
11	23 months	F	<i>Neisseria meningitidis</i>	10.0	—	—	—	Normal
12	6 months	M	—	4.5	2.3	2.9	Ultrasound: normal	Normal
13	19 months	M	<i>Haemophilus influenzae</i>	1.6	4.06	<0.5	Computed tomography, magnetic resonance imaging scans: normal	Mild ataxia
14	7 months	M	<i>Streptococcus pneumoniae</i>	11.8	33.0	0.5	Ultrasound and computed tomography scans: bilateral subdural effusions (right increased density); communicating hydrocephalus	Left focal seizures, mild left weakness
15	8 months	F	<i>Haemophilus influenzae</i>	12.4	0.75	4.0	Ultrasound: widened subdural spaces, echogenic cortical sulci	Normal
16	6 months	M	<i>Neisseria meningitidis</i>	10.1	0.42	3.2	Ultrasound: bilateral subdural effusions, slight ventricular dilatation	Normal
17	6 years	F	<i>Salmonella enteritidis</i>	10.4	2.66	<0.5	Computed tomography scan: mild prominent ventricles, no focal lesion	Normal

Decoder performs real time spectral analysis on the Doppler signals which were recorded on an audio cassette deck (Yamaha KX500). Transcranial Doppler ultrasound examinations were carried out at the bedside when patients were asleep or quiet. CBFV data obtained when patients were uncooperative or unsettled were discarded as movement or crying causes unstable waveforms. Values of the time averaged mean flow velocity, peak systolic velocity, end diastolic velocity, and the resistance index were obtained. Each calculated value was obtained from the mean of the least 10 consecutive cardiac cycles with waveforms of good quality. The outline of the maximum velocity envelope was manually traced on screen using a light pen and the Doppler indices were calculated by software in the Decoder. This method allows accurate waveform measurements to be made while eliminating background noise in the spectrogram or waveforms distorted by patient or probe movement.

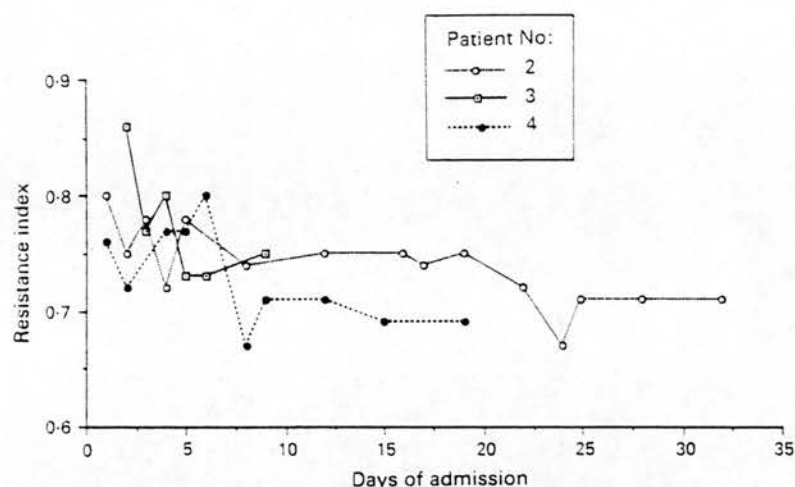


Figure 1 Serial resistance index values in three group I (<3 months old) survivors showing a decrease in resistance index values with clinical improvement. Patient No 2 had a relapse after 10 days of intravenous antibiotics but showed a good response with complete resolution of infection after a further three weeks of treatment. Patient No 4 developed small bilateral subdural effusions which gradually resolved without specific intervention. All three patients had resistance index values within the normal range for age (table 2) at discharge.

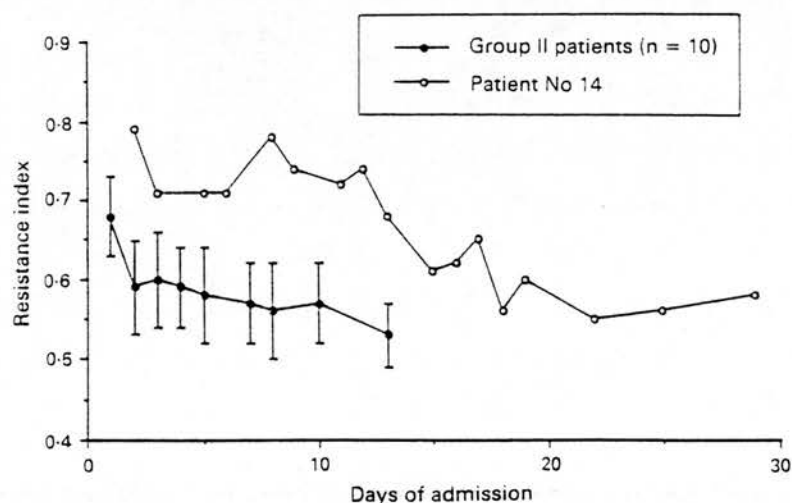


Figure 2 Serial mean (SD) resistance index values from 10 group II patients (older infants and children) who had an uncomplicated recovery while receiving intravenous antibiotics, showing a steady decrease in the mean resistance index with improvement. In contrast, patient No 14 with bilateral subdural effusions and hydrocephalus, who required intrathecal penicillin, had more persistently increased resistance index values which also gradually decreased to the normal range for age with recovery.

Factors known to influence the CBFV waveform include the distal impedance to flow, the carbon dioxide tension (P_{aCO_2}), the calibre of the insonated blood vessel, and the input from the systemic circulation. In this study P_{aCO_2} measurement was not carried out in most of the patients as they did not require ventilatory support; these patients were studied under quiet bedside conditions, breathing spontaneously in room air. In those who were ventilated, P_{aCO_2} was maintained within the normal range (3.5–5.5 kPa). None of our patients had a patent ductus or other congenital heart lesion.

CBFV INDICES

As a ratio, the resistance index, which is equal to the peak systolic velocity minus end diastolic velocity divided by the peak systolic velocity, adapted as an index of cerebrovascular impedance, minimises the error due to a varying angle of insonation. Archer *et al* have shown a significant correlation between decreasing resistance index and decreased distal resistance due to hypercapnia induced vasodilatation.²³ The resistance index is normally higher in neonates and rapidly decreases over the first year of life: the normal range for the first three months is between 0.62 and 0.8 and from later infancy throughout childhood is between 0.4 and 0.62 (see table 2).

Measured values of absolute velocity indices such as the mean flow velocity, peak systolic velocity, or end diastolic velocity are more dependent on variability in the angle of insonation. In a continuous monitoring situation where the transcranial Doppler ultrasound probe is fixed or over short periods of time when there are no changes in its position, a constant angle of insonation may be more reliably assumed. Under these conditions, a reliable correlation has been shown for a percentage change in mean flow velocity and in cerebral blood flow measured using intravenous xenon-133, though correlation for absolute measurements are less reliable due to wide interpatient variations.²⁰

The paired *t* test was used to compare changes between the initial and final (obtained before discharge) CBFV indices in the 16 survivors. Linear correlation between resistance index and mean flow velocity with intracranial pressure, cerebral perfusion pressure, and mean arterial pressure was calculated in five patients where these measurements were available.

Results

RESISTANCE INDEX

In 11 of the patients there was an increased resistance index (greater than the mean plus two standard deviations for age) at the initial transcranial Doppler ultrasound examination (table 3). Serial measurements of the resistance index decreased with resolution of infection and clinical improvement (fig 1, group I; fig 2, group II) and resistance index values were within the normal range at discharge in all survivors (table 3). There was a highly significant decrease in resistance index ($p < 0.001$) from

Table 3 Initial and final cerebral blood flow velocity indices in 16 survivors

Patient No	Age	Initial resistance index	Final resistance index	Initial mean flow velocity (cm/s)	Final mean flow velocity (cm/s)	Initial peak systolic velocity (cm/s)	Final peak systolic velocity (cm/s)	Initial end diastolic velocity (cm/s)	Final end diastolic velocity (cm/s)
2	8 days	0.80	0.71	41.5	43.8	81.0	78.0	16.0	22.0
3	13 days	0.86	0.75	29.3	37.9	67.8	37.9	9.5	16.0
4	11 weeks	0.76	0.69	40.4	68.0	71.3	110.0	17.3	32.4
5	9 months	0.59	0.49	71.7	82.0	109.0	113.0	46.0	57.0
6	8 months	0.66	0.52	55.9	56.9	95.8	81.9	32.8	37.3
7	8 months	0.72	0.61	49.6	70.6	88.5	108.2	25.1	42.6
8	11 months	0.58	0.56	68.2	83.0	108.0	117.0	45.0	51.0
9	26 months	0.67	0.54	65.3	89.8	122.0	129.0	40.4	57.3
10	8 months	0.61	0.50	39.8	85.4	145.4	120.8	56.9	60.6
11	23 months	0.75	0.53	40.9	73.2	80.1	105.5	19.1	48.1
12	6 months	0.64	0.50	68.0	75.4	110.0	106.0	40.0	52.4
13	19 months	0.68	0.60	69.2	57.4	124.0	92.3	40.0	35.0
14	7 months	0.79	0.58	37.2	76.6	80.8	117.8	17.8	49.1
15	8 months	0.69	0.59	67.3	71.0	120.1	112.3	37.9	45.4
16	6 months	0.64	0.55	81.8	77.9	141.2	113.9	49.4	51.0
17	6 years	0.73	0.52	46.3	102.0	98.1	159.6	25.7	73.5
Mean (SD) value		0.70 (0.08)	0.58 (0.08)	57.6 (17.5)	71.9 (16.5)	102.7 (23.8)	108.4 (21.4)	32.4 (14.0)	45.7 (14.6)
p Value		<0.001		<0.01		0.39 (NS)		0.001	

NS=not significant.

paired *t* test analysis of initial and final resistance index values in the 16 survivors. In the group I survivors the mean resistance index decreased from 0.81 to 0.72, and in group II survivors the mean (SD) resistance index decreased from 0.67 (0.06) to 0.545 (0.04). The decrease in resistance index was mainly due to a significant increase in end diastolic velocity (*p*=0.001) rather than to a change in peak systolic velocity (not statistically significant). Figure 2 shows the serial mean (SD) resistance index values of 10 group II patients who responded fully to intravenous antibiotic treatment. In contrast, serial resistance index values were more persistently increased in one patient with subdural effusions who required five doses of intrathecal penicillin in addition to intravenous antibiotics. There was no difference in the pattern of resistance index change between group I and II patients.

MEAN FLOW VELOCITY

Three patients had an initial mean flow velocity less than the normal range for age.²² Overall, the final mean flow velocity in the 16 survivors was significantly increased compared with the initial mean flow velocity (*p*<0.01) on paired *t* test analysis, which may suggest an overall increased mean cerebral blood flow with recovery from infection compared with initial values at admission. Two patients in our study had a mean flow velocity >120 cm/s on one occasion each; patient No 11 on day 3 (120.2 cm/s) and patient No 17 on day 2 (132.3 cm/s). The increased mean flow velocity values did not persist in these two patients, however, and were within the normal range on the next day. In individual patients serial mean flow velocity values on a day to day basis were more variable

compared with a more consistent decreasing pattern for serial resistance index values.

CHANGES IN CBFV DUE TO MANNITOL

In three patients simultaneous transcranial Doppler ultrasound and intracranial pressure recordings were carried out on the day of admission before and after mannitol infusions (table 4). In these patients the cerebral perfusion pressure increased as the intracranial pressure decreased after the mannitol infusions with accompanying improvement in CBFV indices, as the resistance index decreased and mean flow velocity increased. In patient No 16 lumbar puncture was deferred until after the mannitol infusion when the resistance index had decreased from 0.64 to 0.59, and the mean flow velocity increased from 81.8 to 96.9 cm/s.

CASE DESCRIPTIONS

Patient No 15 was admitted in a drowsy and lethargic state with a marked bulging fontanelle. At diagnostic lumbar puncture, the cerebrospinal fluid pressure measured by a non-displacement strain gauge pressure transducer method (Gaeltec Ltd) was increased with C waves at a mean of 19 mm Hg, and the cerebral perfusion pressure was 53 mm Hg. With a mannitol infusion over 30 minutes and a bolus dose of intravenous frusemide while leaving the spinal needle in position, the cerebrospinal fluid pressure gradually decreased to 10 mm Hg. After the mannitol infusion, the resistance index decreased from 0.69 to 0.60 and the mean flow velocity had increased from 68.1 to 91.6 cm/s when the cerebral perfusion pressure had increased to 62 mm Hg.

Table 4 Changes in intracranial pressure, cerebral perfusion pressure, and CBFV indices before and after mannitol infusions in four patients. Values given as before mannitol/after mannitol

Patient No	Age	Mean arterial pressure (mmHg)	Intracranial pressure (mmHg)	Cerebral perfusion pressure (mmHg)	Resistance index	Mean flow velocity (cm/s)	Peak systolic velocity (cm/s)	End diastolic velocity (cm/s)
11	23 months	69/68	28/10	41/58	0.82/0.67	36.7/59.0	78.5/106.0	12.2/34.4
15	8 months	72/72	19/10	53/62	0.69/0.60	68.1/91.6	120.1/139.1	37.1/54.5
16	6 months	81/62	—/17	—/45	0.64/0.59	81.8/96.9	141.2/156.0	49.4/61.7
17	6 years	65/77	28/10	37/67	0.73/0.51	46.3/132.3	98.1/197	25.7/98.8

Patient No 17 was admitted in an unconscious state, only flexing to pain with upward ocular deviation. An emergency computed tomography scan was reported to show only mildly prominent ventricles with mild communicating hydrocephalus, no focal lesions, and no evidence on scan of significant cerebral oedema or increased intracranial pressure. Her initial resistance index of 0.73 was markedly increased, however, and the initial mean flow velocity of 46.3 cm/s was also much reduced for her age. Lumbar puncture was performed with caution using the technique as described; the opening cerebrospinal fluid pressure was increased at a mean of 28 mm Hg with C waves and a wide pulse pressure, and the cerebral perfusion pressure was only 37 mm Hg. The spinal needle was removed only when the cerebrospinal fluid pressure had decreased gradually to 6 mm Hg over an hour with mannitol infusion and frusemide, and intermittent small incremental drainage of cerebrospinal fluid. Twelve hours later at repeat lumbar puncture, the cerebrospinal fluid pressure had decreased to 10 mm Hg, the resistance index had decreased to 0.51, and the mean flow velocity was 132.3 cm/s. Figure 3 shows the cerebrospinal fluid pressure recordings, cerebral perfusion pressure, and corresponding CBFV indices at the initial and repeat lumbar puncture 12 hours later.

Overall in these four patients there was a significant correlation between resistance index and intracranial pressure ($r=0.81$; $p<0.05$), resistance index and cerebral perfusion pressure ($r=-0.9$; $p<0.01$), and mean flow velocity and cerebral perfusion pressure ($r=0.88$; $p<0.01$). There was no significant correlation between resistance index and mean arterial pressure, or mean flow velocity and mean arterial pressure.

PRESSURE PASSIVITY

A 2 week old girl (patient No 1) with group B

haemolytic streptococcal meningitis and septicaemia required early ventilation and inotrope support in addition to systemic antibiotics, dexamethasone, and anticonvulsants for an increasing frequency of apnoeic episodes and a poor peripheral circulatory state. A cerebral ultrasound scan showed collapsed lateral and third ventricles with increased echogenic areas in both parietal regions, suggesting the presence of cerebral oedema and focal areas of intracranial haemorrhage or infarcts. Through a subarachnoid catheter the initial intracranial pressure measured was 6 mm Hg, whereas the mean arterial pressure was 50 mm Hg.

She remained unstable with frequent bradycardic episodes and there were intermittent increases of intracranial pressure to 20–30 mm Hg, despite mannitol. There was further deterioration over the next two days with a labile systemic blood pressure and frequent hypertensive and bradycardic episodes. On the third day of admission her electroencephalogram showed electrocerebral silence, her pupils were unresponsive, and she died the next day. Transcranial Doppler ultrasound recordings showed that she had a pressure passive CBFV response to changes in systemic blood pressure (fig 4) with a significant linear correlation between resistance index and mean arterial pressure ($r=-0.69$; $p<0.02$), which may suggest loss of cerebrovascular autoregulation. Necropsy confirmed congested and swollen cerebral tissue, a compressed ventricular system and thrombosed vessels over both temporal poles with intraparenchymal and subarachnoid haemorrhages.

In contrast, the other two patients who also required intensive care support and treatment for intracranial hypertension did not show a pressure passive CBFV response. This suggests that no loss of cerebrovascular autoregulation occurred during the acutely ill stage in these two patients.

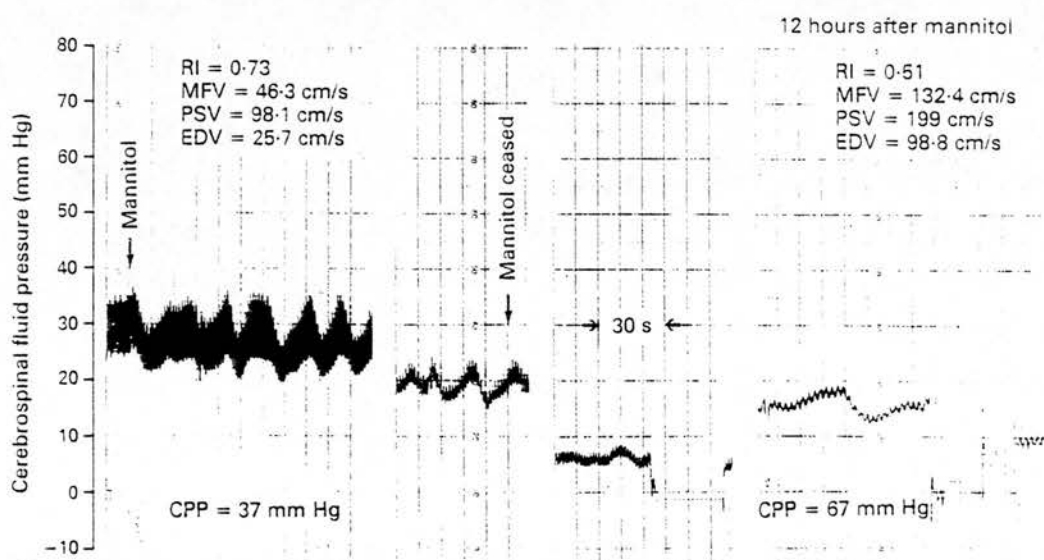


Figure 3 Cerebrospinal fluid pressure recordings with accompanying cerebral perfusion pressure (CPP), resistance index (RI), and mean flow velocity (MFV) values at initial and repeat lumbar puncture (12 hours after mannitol infusion) in a 6 year old patient with salmonella meningitis (patient No 17). The cerebrospinal fluid pressure had decreased from 28 to 10 mm Hg. Cerebral perfusion pressure increased from 37 to 67 mm Hg, with an accompanying decrease in resistance index from 0.73 to 0.51 and increase in mean flow velocity from 46.3 to 132.3 cm/s. EDV=end diastolic velocity, PSV=peak systolic velocity.

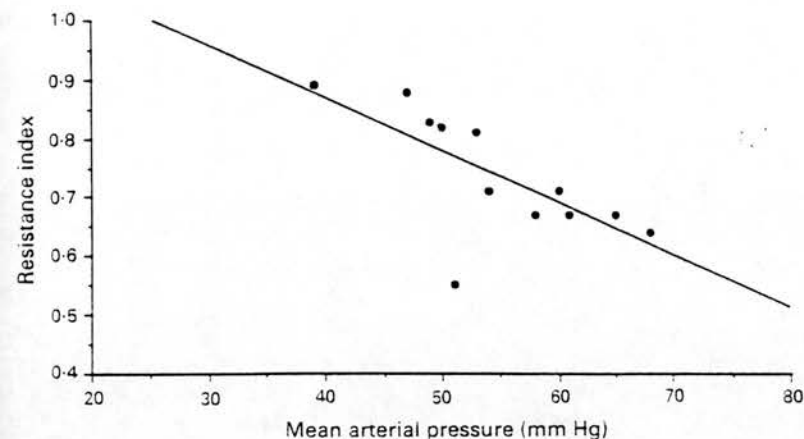


Figure 4 Plot of resistance index against mean arterial pressure values from a 2 week old infant with group B haemolytic streptococcal meningitis who died (patient No 1). This shows a pressure passive CBFV response with a significant linear correlation between resistance index and mean arterial pressure suggesting loss of cerebrovascular autoregulation. $y = 1.2252 - 8.9354e-3x$, $R^2 = 0.476$, $r = -0.69$, $p < 0.02$.

SUBDURAL EFFUSIONS

Three patients who developed bilateral subdural effusions were regularly monitored; fig 5 shows serial resistance index changes during their admission. Two patients who had small bilateral subdural effusions showed a subsequent increase in their resistance index before later settling down to normal values for age. They did not require drainage or other specific treatment.

In patient No 14, viable pneumococci were cultured from the cerebrospinal fluid obtained by subdural tap, despite adequate doses of intravenous penicillin and cefotaxime. Cranial ultrasound and computed tomography scans showed a communicating internal hydrocephalus and bilateral subdural collections (which had persisted after a recent *H influenzae* meningitis infection) with increased scan density of the right subdural collection. Thus five daily doses of intrathecal penicillin were given until cultures were negative. Serial resistance index values were more persistently increased in this patient but gradually returned to normal range; the mean flow velocity was less than the normal range on the first day only and increased with recovery. Neurosurgical intervention was not

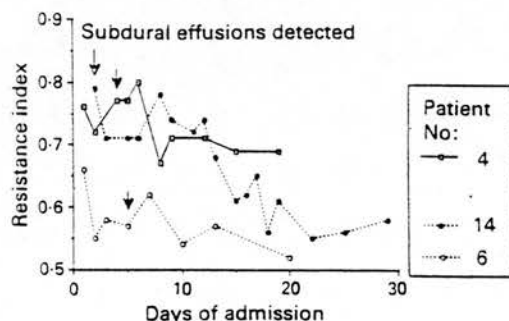


Figure 5 Serial resistance index values from three patients with subdural effusions (arrows) which shows a transient increase in resistance index values after an initial decrease with early clinical response to antibiotics. Further decreases in resistance index values with a gradual return to normal values for age suggested no significant cerebral perfusion compromise and neurosurgical drainage was not required in all three patients. Patient No 14 also had a communicating hydrocephalus; he required five doses of intrathecal penicillin until the subdural fluid culture was confirmed to be negative.

required and he showed good clinical improvement with resolution of pyrexia and irritability. Sequelae in this patient were focal left sided seizures which were easily controlled by phenytoin and a mild left hemiparesis which was rapidly resolving by the time of discharge.

Discussion

The pathogenesis of cerebral injury in bacterial meningitis is a complex interaction of a number of inflammatory processes which leads to brain oedema, increased intracranial pressure, and decreased cerebral perfusion.³ Cerebral oedema may occur early^{5,24} and may be vasogenic, cytotoxic, or interstitial in origin. The inflammatory effects on the cerebral microvasculature and macrovasculature can cause arteritis, cortical thrombophlebitis leading to thrombosis, vasospasm, and stenosis with further risk of secondary cerebral infarction or ischaemia.²⁵ If the large cerebral arteries are affected there may be serious neurological complications and a poor outcome.²⁶ Ventriculomegaly and subdural collections are well recognised complications.²⁷

No single modality of monitoring can provide all the required information for understanding the complex balance of intracranial haemodynamic and hydrodynamic processes occurring in ill children with meningitis. Although the need for invasive continuous monitoring of intracranial pressure, cerebral perfusion pressure, or cerebral metabolism is seldom in doubt for the very sick or comatose patient, most children with meningitis do not require intensive care management. In such children, however, a non-invasive means of early detection of deterioration in cerebral haemodynamic trends may help in guiding optimal management. Increased intracranial pressure is still a common feature in the early phase in those who are only moderately ill⁶ and prompt treatment to reduce intracranial pressure—for example, with mannitol—may help prevent further insult from reduced cerebral perfusion pressure. Some patients may develop secondary complications such as subdural effusions, hydrocephalus, or vasculitis and vasospasm and it would be important to monitor the consequent haemodynamic effects of these complications. Xenon computed tomograms have been reported to provide information on regional perfusion states as well as absolute levels of perfusion in meningitis²⁸ but cannot be frequently repeated, particularly in young children, because of the risks of radiation exposure. A recent report has suggested that cerebral blood flow itself may be rapidly changing during the process of xenon computed tomography due to xenon induced vasodilatation.²⁹

CEREBRAL BLOOD FLOW VELOCITY INDICES

As an increased resistance index has been shown to be significantly related to increased intracranial pressure^{10,11,18,19} our results suggest that most of our patients had increased intracranial pressure in the early stages of meningitis as the resistance index was significantly increased compared with final predischarge values. With

recovery, the final resistance index values decreased due to a significant increase in the end diastolic velocity with no significant change in the peak systolic velocity. The increased resistance index was thus mainly due to a decreased end diastolic velocity, most likely reflecting increased distal cerebrovascular resistance. This supports the view that in the initial phase increased intracranial pressure is a significant contributing factor to compromised cerebral perfusion through increased cerebrovascular resistance. Lundar *et al* have also reported from their patients who required neurointensive monitoring that in severe intracranial hypertension when the cerebral perfusion pressure became critically low (less than 40 mm Hg), CBFV waveforms became increasingly pulsatile as systolic blood velocity increased, whereas the diastolic blood velocity was reduced.²¹

Although most of our patients had an initial mean flow velocity within the normal range for their age, there was a significant overall increase in the final values when recovered, associated with a decreased resistance index, thus suggesting that the mean cerebral blood flow may have been relatively reduced initially. With no knowledge of the true middle cerebral artery diameter and wide interpatient variations, however, absolute values of mean flow cannot be determined by this technique, nor can interpatient comparisons be made. It is thus more reliable to use serial CBFV indices to chart haemodynamic trends for each individual patient.

AGE EFFECT: NEONATES VERSUS OLDER INFANTS AND CHILDREN

In contrast with the differences in CBFV changes in the two age groups reported by McMenamin and Volpe,¹⁵ we found no difference in the pattern of cerebral haemodynamic change between our very young infants and the older group. They suggested the neonatal brain's lesser tendency to respond to infection with oedema, together with a more compliant neonatal cranium as two possible reasons for the absence of increased intracranial pressure in this group. Intracranial pressure in their study was indirectly measured by a transfontanometric method which may be at variance with directly measured levels of intracranial pressure. Necropsy findings on the 2 week old patient (patient No 1) described earlier illustrate that intracranial hypertension and impaired perfusion can be an equally significant complication of meningitis in very young infants with the therapeutic implication that careful attention to the maintenance of adequate cerebral perfusion is just as important at this age.

CBFV CHANGES DUE TO MANNITOL

In all four patients studied there was an improvement in CBFV indices after mannitol infusion. Apart from its osmotic effect in reducing the brain water content, mannitol also reduces blood viscosity and increases local cerebral blood flow.³⁰ Decreased resistance index and increased mean flow velocity after

mannitol infusion suggests that cerebral perfusion was enhanced in these patients with a reduction in impedance to flow.

PRESSURE PASSIVITY

We report the occurrence of a pressure passive CBFV response to systemic mean arterial pressure changes only in the neonate who died, suggesting that loss of cerebrovascular autoregulation may be a poor prognostic indicator for survival. Loss of cerebrovascular autoregulation has been reported in a rabbit model with experimental pneumococcal meningitis³¹ and has been previously recognised to be an important link in the pathophysiology of intracranial haemorrhage and cerebral ischaemia in distressed premature infants.³² Close attention to maintaining normal levels of systemic blood pressure is therefore required when a pressure passive CBFV response suggests loss of cerebrovascular autoregulation.

In contrast, Ashwal *et al* reported from their cases with bacterial meningitis that autoregulation was preserved while cerebral blood flow or carbon dioxide reactivity varied among patients and in different regions of the brain in the same patient.²⁸ Overall intact autoregulation was assumed in 18 patients as cerebral blood flow values were normal within a range of mean arterial blood pressures from 56 to 102 mm Hg, though only single measurements from each individual patient were plotted. With only one or two measurements available on most patients due to limitations of repeatability with the xenon computed tomography technique, it may not be entirely reliable to extrapolate that autoregulation would be maintained through a similar systemic arterial pressure range in all patients. Similarly, conclusions on carbon dioxide reactivity in this study were based on only two separate measurements each in seven patients. Data reported by Kirkham from patients with non-traumatic coma where carbon dioxide reactivity was assessed by changes in mean flow velocity suggest that analysis of the shape of the carbon dioxide reactivity curve may be helpful in predicting poor outcome.³³ Lundar *et al*, also using transcranial Doppler ultrasound monitoring, reported four patients with poor outcome who also showed pressure passivity in addition to loss of carbon dioxide reactivity.²¹ Only by monitoring haemodynamic changes over a range of systemic arterial pressure and PaCO_2 changes for each individual patient can we be certain of the likely cerebrohaemodynamic effects on each patient of therapeutic manoeuvres to alter these factors as there is a complex balance of hydrodynamic and haemodynamic factors in each instance. Transcranial Doppler ultrasound thus provides a practical means of immediate assessment of cerebral haemodynamic carbon dioxide reactivity and autoregulation mechanisms in critically ill patients. Calculated cerebral perfusion pressure changes (derived from mean arterial pressure and intracranial pressure alone do not always reliably predict cerebral blood flow changes; for example, hyperventilation increases the cerebral perfusion pressure by reducing the intracranial

pressure as a result of reducing cerebral blood flow through vasoconstriction. Ashwal *et al* highlighted the risk that increasing cerebral perfusion pressure through hyperventilation can paradoxically cause ischaemic insult: when cerebral perfusion levels may already be compromised.²⁸

VASOSPASM

Vasculitis causing vasospasm or stenosis leading to further thrombotic, ischaemic damage may occur as a later complication during the acute phase. Mean flow velocity values in any of the basal cerebral arteries which are markedly increased, especially if asymmetric, may be suggestive.¹⁶ Further transcranial Doppler ultrasound examinations would be indicated to determine whether abnormal mean flow velocity values are persistent as alternative invasive investigations such as angiography would be risky in ill children. In many centres magnetic resonance imaging angiography may not be readily accessible. None of our patients had persistently increased mean flow velocity values and thus we assume that none had significantly large cerebral artery stenosis or vasospasm. It is not possible to be certain if the transient increased mean flow velocity values detected in two of our patients were due to transient vasospasm or increased mean flow but neither had any focal clinical signs of ischaemia and the two patients were clinically improving. All our surviving patients had a good outcome with no serious neurological handicap at discharge.

VENTRICULAR DILATATION/SUBDURAL EFFUSIONS

Computed tomography has a limited role in early meningitis.³⁴ Changes associated with increased intracranial pressure or early cerebral oedema may not be present on early scans as illustrated by one of our patients (patient No 17) and thus a relatively normal scan may be falsely reassuring. Kline and Kaplan reported that although there were abnormal computed tomography findings in 20 of 25 children with bacterial meningitis, the yield of information that was either diagnostically or therapeutically useful was low; positive findings of obvious clinical relevance were only present in two patients.³⁵ It may be difficult without accompanying haemodynamic or intracranial pressure data to assess if the clinical significance of complications detected by computed tomography or ultrasound scans, such as hydrocephalus or extra-axial fluid collections, warrant further invasive investigations or management such as surgical shunting or drainage procedures, which are not always appropriate in children with bacterial meningitis.²⁷ In our patients with subdural effusions serial CBFV monitoring suggested that there was no significant perfusion compromise as the resistance index decreased to the normal range. Serial resistance index measurements in individual patients can be a reliable indicator for shunting and monitoring cerebrohaemodynamic changes after effective cerebrospinal fluid drainage or diversion.^{10 11}

Our results suggest that serial CBFV changes provide useful information on cerebrohaemo-

dynamic trends in individual children, but careful interpretation of CBFV indices is required for children with meningitis where the pathophysiology is complex. In our experience, as transcranial Doppler ultrasound is a blind technique, the resistance index was more reliable for serial measurements performed on different days as it is, of course, difficult to be certain of always placing the probe on exactly the same position or of insonating the vessel at an identical angle at every examination and thus significant error of measured CBFV changes due to a variable angle of insonation can be wrongly interpreted as true flow velocity changes.³⁶ In the early phase when increased intracranial pressure may be present, the resistance index is more useful and resistance index values greater than 0.65 for older infants and children and greater than 0.8 in neonates and young infants suggest that there may be significant perfusion compromise, especially when mean flow velocity values are also less than normal. Reported values suggesting increased resistance index in different clinical conditions^{10 11 18 37} as well as reported normal ranges appear to be fairly similar and reproducible, supporting this as a reliable index.

We did not find serial monitoring of mean flow velocity from day to day to be as consistent in our patients, but suggest that this index would be more useful as a means to detect and monitor complications of basal cerebral artery vasospasm or stenosis. Repeated examinations with left/right comparisons can be made, especially if focal signs are clinically detected. In the intensive care situation where a transcranial Doppler ultrasound probe can be left in a fixed position, mean flow velocity changes may then be a reliable guide to changes in mean volume flow over a short period for assessment of pressure passivity or carbon dioxide reactivity,²¹ assuming that no significant change in calibre of the insonated vessel is likely to occur.

In summary, we report that improvement in cerebral blood flow velocity with decreased resistance index due to increased end diastolic velocity and increased mean flow velocity occurs with resolution of pyogenic meningitis. This suggests that relatively decreased perfusion may occur during the acute phase in children with meningitis who are only moderately ill. Increased intracranial pressure causing increased cerebrovascular resistance is likely to be a significant contributing factor. There was no difference in CBFV patterns of neonates or older infants and children, emphasising that equally careful attention to factors which influence cerebral perfusion is required for neonatal patients who generally have a much poorer outcome.¹ Loss of cerebrovascular autoregulation as shown by a pressure passive CBFV response may be a poor prognostic indicator. We suggest that transcranial Doppler ultrasound can be a useful non-invasive method of monitoring cerebral haemodynamic changes in children with meningitis.

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Cerebrovascular resistive index assessed by Duplex Doppler sonography and its relationship to intracranial pressure in infantile hydrocephalus

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Abstract. Duplex Doppler sonography and direct intracranial pressure (ICP) measurement were performed on 18 patients with infantile hydrocephalus. ICP was measured through a frontal reservoir or ventricular tap using a nondisplacement pressure transducer. The Pourcelot Resistive Index, $RI = (\text{peak systolic} - \text{end diastolic}) / \text{peak systolic velocity}$ was obtained from pulsed-wave Doppler measurements of blood flow velocity in the anterior (ACA) and/or the middle cerebral (MCA) arteries. There was a statistically significant positive correlation between ICP and RIs in the MCA and ACA. Paired RI measurements in 7 patients with raised ICP decreased significantly from a mean of 0.90 pre-tap to 0.75 post-tap. Our results suggest that the RI provides a reliable measure of cerebrovascular resistance in hydrocephalus. Duplex Doppler ultrasonography thus is a useful noninvasive means of monitoring cerebrohaemodynamic change with simultaneous imaging of ventricular size in infantile hydrocephalus.

Infantile hydrocephalus is an important clinical problem with reported incidence figures ranging from 2–15 per 10,000 live births [1]. While the proportion associated with myelomeningocele is decreasing, posthaemorrhagic hydrocephalus in preterm neonates has become an increasing problem. However, regardless of the underlying aetiology active hydrocephalus associated with raised intracranial pressure (ICP) and progressive ventricular dilatation can cause secondary neurologic deficit as a result of reduced cerebral perfusion and ventricular dilatation per se [2]. Assessment of cerebral hydrodynamics and haemodynamics is thus ideal at initial assessment and may need to be repeated in some patients.

Duplex Doppler ultrasonography provides a non-invasive method for assessing changes in cerebral blood flow velocity simultaneously with cerebral imaging in infants with an open anterior fontanelle. The Pourcelot Resistive Index [3], $RI = (S-D)/S$ where S is the maximum systolic velocity and D is the minimum diastolic velocity, was first adapted by Bada et al. [4] as an index of cerebrovascular

resistance in neonates. As a ratio, the RI minimises the effect of a variable angle of insonation. Archer et al. [5] have shown in normal infants that hypercapnia induced cerebral vasodilatation with decreased distal cerebrovascular resistance was associated with a decreased RI. Absolute velocity measurements such as the mean flow velocity, peak systolic or end-diastolic velocity may be less reliable as error due to a variable angle of insonation may be considerable when the course of the cerebral arteries can be significantly distorted by ventricular distension in hydrocephalus [6].

Previous Doppler studies in infantile hydrocephalus [7–10] have reported conflicting conclusions on the significance of the RI. None of these studies have related direct measurement of intracranial pressure (ICP) to observed RI in patients with infantile hydrocephalus, although Seibert et al. [10] did illustrate a correlation between RI and cerebral perfusion pressure in an experimental canine model. The aim of our study was to assess the relationship between RI measured by duplex Doppler ultrasonography with simultaneous direct ICP measurement in infants with hydrocephalus.

Patients and methods

Eighteen infants (11 male, 7 female); twelve were neonates, six between 4–11 months of age, underwent direct ICP and duplex Doppler ultrasound assessment at presentation when there was clinical suspicion of raised ICP or evidence of increasing ventricular dilatation. The aetiology of hydrocephalus was posthaemorrhagic in 8, post-meningitic in 1, associated with myelomeningocele in 1, and of congenital origin in 8. Ventricular dilatation was moderate in 4 and severe in 8 patients.

ICP was directly measured from the ventricular compartment with a non-displacement strain gauge pressure transducer (Gaeltec Ltd) through ventricular taps ($n = 12$) or percutaneous puncture of a frontal reservoir ($n = 6$). It is our usual clinical practice to insert a separate frontal reservoir [11] to have access for direct ICP measurements or cerebrospinal fluid (CSF) drainage in patients who may require repeated measurements or taps. If the ICP was elevated, cerebrospinal fluid (CSF) was drained till ICP returned to the normal range for age [12].

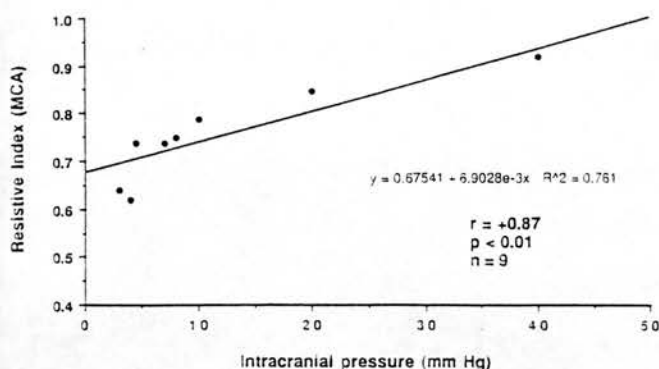


Fig. 1. Resistive index from the middle cerebral artery (MCA) plotted against intracranial pressure (ICP) measurements ($r = 0.89$, $p < 0.01$).

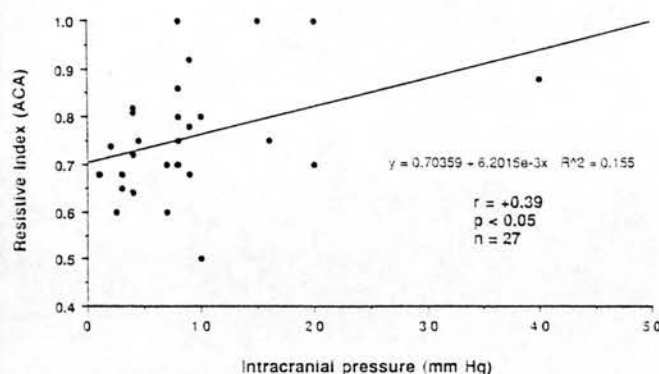


Fig. 2. Resistive index (RI) from the anterior cerebral artery (ACA) plotted against intracranial pressure (ICP); $r = +0.39$, $p < 0.05$.

Cerebral blood flow velocity measurements were simultaneously performed from the anterior cerebral artery (ACA) and/or the middle cerebral artery (MCA) using range-gated pulsed-wave Doppler from a US Diasonics DRF 400 machine with a range of 3.5–7.5 MHz probes. The ACA was imaged through the anterior fontanelle, with the Doppler probe placed in its distal segment at the anterior bend of the corpus callosum in the midline sagittal plane. The MCA was studied from the temporal position which optimises the intensity of the signals received as the angle of insonation is minimal. The RI was calculated by the incorporated software from the formula as described previously.

Correlation (r) between ICP and RI measured in the ACA and the MCA were separately determined and the t -test was used to assess significance, set at conventional levels i.e. at the 5% level. RI measurements before and after CSF taps were compared using the paired t -test.

Results

A total of 36 corresponding RI and ICP data pairs (ACA-27, MCA-9) were available in 18 patients. Mean (± 1 standard deviation) RI was 0.79 (0.14) in the ACA and 0.79 (0.11) in the MCA. Reported normal RI reference values are 0.77 (0.09) for preterm infants (< 33 weeks gestation) and 0.71 (0.07) for term infants, decreasing to 0.5 by the first year of life [13]. The initial RI in most of our patients was raised compared to the mean normal RI values for age. There was a statistically significant positive correlation between ICP and RI in both cerebral arteries; more

reliably from the MCA. ($r = +0.89$, $p < 0.01$ – Fig. 1); ACA ($r = +0.39$, $p < 0.05$ – Fig. 2).

Seven patients with raised ICP had 10 paired RI measurements from the same cerebral artery performed before and after CSF drainage. Pre-drainage mean (sd) ICP was 15.8 (11.5) mm Hg and post-drainage mean ICP was 6.2 (2.0) mm Hg; ($p = 0.05$). In these patients the mean (sd) RI decreased significantly from 0.90 (0.08) pre-tap to 0.75 (0.07) post-tap ($p = 0.001$, Fig. 3).

Case illustration: Patient SB, a 2-week-old term infant with hydrocephalus associated with a myelomeningo-coele had an elevated opening ICP of 20 mm Hg and RI in the ACA was 1.0 (i.e. no diastolic flow). Ten mls of CSF was drained via a ventricular tap and ICP decreased to 7 mm Hg with return of diastolic flow and an RI of 0.7 post-tap. Figures 4a, b show the pre- and post-tap Doppler studies and Fig. 5 shows the corresponding ICP recording and RI values.

There was no relationship between the severity of ventricular dilatation and the ICP or RI values. Two patients who had the most severe and similar degree of ventricular dilatation had greatly different flow velocity and ICP dynamics. One patient with progressive hydrocephalus had a markedly elevated ICP of 40 mm Hg and RIs were 0.92 and 0.88 suggesting significant cerebral perfusion compromise. The other patient with stable ventricular dilatation associated with an arachnoid cyst had a normal opening ICP of 4 mm Hg and RIs were 0.66 and 0.62 which suggests adequate intracranial volume/ICP buffering and little impairment of perfusion.

Discussion

Progressive hydrocephalus leads to macro- and microvascular distortion, compression and reduction in vessel calibre with decreased cerebral blood flow and eventual tissue destruction [2]. Raised CSF xanthine and hypoxanthine levels during sleep recordings in hydrocephalic patients with significant periods of raised ICP provide metabolic evidence of hypoxic ischaemia due to impaired

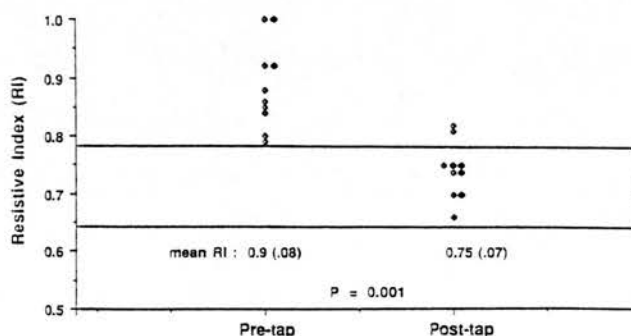


Fig. 3. Ten paired RI measurements pre- and post-tap from 7 patients with raised intracranial pressure showing a significant decrease in RI after cerebrospinal fluid drainage. The horizontal lines represent the mean ± 1 standard deviation RI values for term neonates [13]. Mean RI further decreases with age.

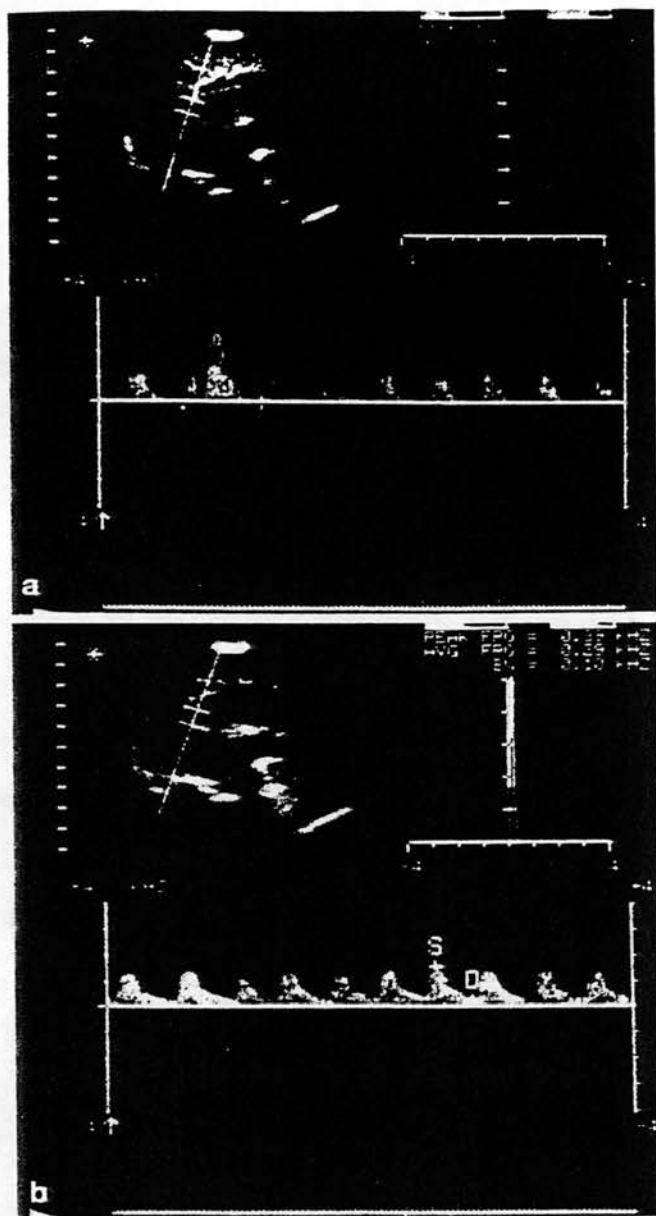


Fig. 4a, b. Duplex Doppler studies from the anterior cerebral artery in patient SB, a 2-week-old infant with myelomeningocele. Before CSF drainage (a), there was no end-diastolic flow detected. After 10 ml CSF was drained (b), there was return of diastolic flow

cerebral perfusion [14]. Prolonged mean transit times of isotope clearance suggesting a reduced circulatory reserve has also been shown to be significantly related to reduced cerebral perfusion pressure [15]. These studies are however time-consuming and invasive. Measurement of cerebral perfusion using radioisotopes such as Xenon 133 cannot justifiably be regularly repeated for monitoring purposes in young infants.

In our study we have found an elevated RI in most of our patients in common with most studies except Grant et al. [8] who reported no significant difference in their hydrocephalic patients. In patients with hydrocephalus the RI can clearly be within normal range if ICP is not elevated, such as in those not requiring shunting, or asymptomatic

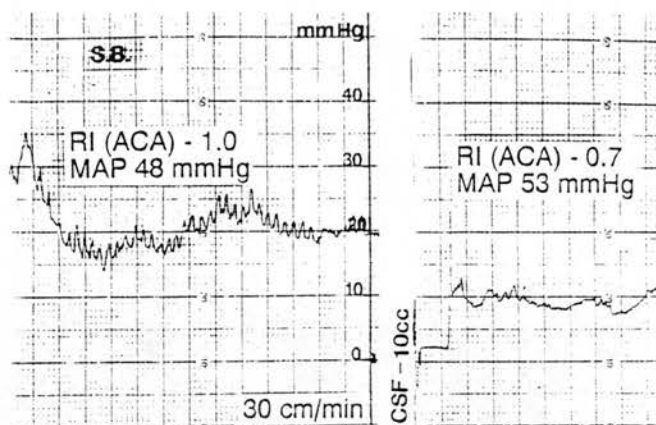


Fig. 5. Corresponding intracranial pressure (ICP) and RI measurements before and after CSF drainage in patient SB. Pre-drainage ICP and RI were 20 mmHg and 1.0 respectively i.e. no diastolic flow; post-drainage ICP decreased to 10 mmHg and RI increased to 0.7 with return of diastolic flow

shunted patients with functioning shunts with presumably little compromise in cerebral perfusion [13]. We have shown a significant positive correlation between increased direct intraventricular pressure measurements and increased RIs in the ACA and MCA, the two most easily accessible basal cerebral arteries by duplex ultrasound. In addition, we have shown that after CSF volume drainage, there was a highly significant decrease in RI as distal resistance to flow is reduced with decrease in ICP. While we do not suggest that the RI is an alternative measure of ICP or cerebral perfusion pressure, our results nevertheless support the view that the RI does serve as an index of cerebrovascular resistance in patients with hydrocephalus. It can thus provide a noninvasive means of assessing cerebrohaemodynamic change for individual patients with hydrocephalus where there is a complex interaction of CSF hydrodynamic factors, the residual buffering capacity and cerebrohaemodynamic reserve.

Hill and Volpe [7] first reported an abnormally high RI in the ACA in infantile hydrocephalus. Nine of their 11 patients had raised ICP measured by a transfontanometric method. They however concluded that ventriculomegaly was probably a more critical factor than raised ICP in the pathogenesis of impaired blood flow as 2 patients in their study with normal ICP but marked ventriculomegaly had elevated RI and patients with the most significant ventriculomegaly had the highest RI measurements. However, as their ICP measurements were done by a transfontanometric method there may have been some variance from true intraventricular pressure levels. Our results do not suggest that ventricular dilatation per se is responsible for impaired cerebral perfusion as we found no correlation between ventricular size and RIs or ICP levels. The intracranial volume/ICP compensation or buffering capacity is more likely to be variable between individual patients depending on the stage of progression and other factors influencing CSF dynamics such as the outflow resistance. Thus assessment of clinical symptoms and measurements of ICP, RI and ventricular size has to be specifically evaluated for each patient.

Van Bel et al. [9] also found an elevated RI in neonatal posthaemorrhagic hydrocephalus which however was due mainly to increased peak systolic flow velocity with no significant change in end diastolic velocity after CSF drainage. They concluded that the elevated RI was due an increase in vascular compliance with no significant change in cerebrovascular resistance at that stage. No attempt was made to measure ICP at all in this study which they assumed was likely to be normal "because their patients were all studied at an early stage of posthaemorrhagic hydrocephalus (3–33 days)". However, Kaiser and Whitelaw [16] have shown that significantly higher direct ICP levels were associated with progressive increase in ventricular size in posthaemorrhagic hydrocephalus. Thus it was not possible to determine what effect ICP, which has a critical influence on cerebral perfusion, had on observed Doppler values in patients from Van Bel's study. Using transcranial Doppler ultrasonography we have shown in a separate study a significant decrease in RI due to an increase in end-diastolic velocity with decrease in ICP after CSF taps and ventricular shunting [17]. This supports our observations in this paper that the RI is a reliable index of distal resistance.

The cerebral arterial velocity waveform and thus the RI can be affected by other non-intracranial factors such as a patent ductus arteriosus [18], polycythaemia [19] and changes in intrathoracic pressure eg. pneumothorax [20]. Most of these factors are less of a problem outwith the pre-term and neonatal period and all our patients were in a stable condition at the time of assessment without significant cardiovascular or respiratory instability. Cerebral perfusion changes as a result of change in ICP occur mainly through changes in distal resistance vessels, with pial arterial dilatation to maintain cerebral blood flow as ICP increases with resultant decrease in cerebral perfusion pressure. It is thus assumed that changes in the ACA and MCA velocity waveforms in this study are not likely to be due to alteration in the calibre of both these major cerebral arteries at the point of insonation but as a result of flow changes effected by change in distal resistance vessels. Although flow velocity indices do not represent true volume flow in different individuals, serial changes in RI may still be a reliable index of change in cerebrovascular resistance for individual patients.

Clinical signs and symptoms of raised ICP are often unreliable [21] and management in the early stages particularly of posthaemorrhagic hydrocephalus may require repeat CSF taps and direct ICP measurement. In some cases the hydrocephalic process may arrest spontaneously reaching an equilibrium with adequate compensation and no further perfusion compromise. Shunting would then not be indicated as the risks of shunt-related complications such as infection, blockage and overdrainage are not inconsiderable. Duplex Doppler ultrasonography thus provides us with a noninvasive and easily repeatable means of monitoring for further increase in ventricular size as well as a method of monitoring cerebrohaemodynamic change. This could be helpful in determining the need for further CSF taps or ventricular shunting [13]. Shunted patients will also require further monitoring for adequacy of shunt function. At follow-up cranial ultra-

sound examinations, change in ventricular size after shunting can be measured and in addition serial RIs can provide an index for monitoring cerebrohaemodynamic change. Serial measurements of a cerebral blood flow velocity response to CSF volume manipulation may provide an indicator of volume buffering reserve over time in individual patients [22]. However, further work is still needed to define clear guidelines for the use of RI or other Doppler indices in the clinical management of infantile hydrocephalus in particular to assess whether further progression or arrest is occurring in individual cases.

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CEREBRAL BLOOD-FLOW VELOCITY AND INTERMITTENT INTRACRANIAL PRESSURE ELEVATION DURING SLEEP IN HYDROCEPHALIC CHILDREN

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Sleep has long been recognised to be a useful physiological challenge to distinguish intermittent active from compensated hydrocephalus, since intracranial pressure (ICP) elevations have been noted to occur particularly during rapid eye-movement (REM) sleep and also in stage 2 non-REM sleep (Cooper and Hulme 1966, Di Rocco *et al.* 1975, Minns 1979). Elevations occur in patients with normal awake resting ICP levels (Di Rocco *et al.* 1975), as well as in those with a clinical diagnosis of arrested hydrocephalus (Whittle *et al.* 1985). The clinical importance of these episodic elevations of ICP during sleep is not entirely clear, although prolonged ICP measurements are evaluated in making decisions on shunting procedures for patients with chronic or clinically 'compensated' hydrocephalus (Mori *et al.* 1986).

A major concern is the secondary ischaemic insult due to significant impairment of cerebral perfusion which may occur during sustained elevation of ICP. The transcranial Doppler ultrasound (TCD) technique described by Aaslid *et al.* (1982) provides a non-invasive method of repeatedly measuring cerebral blood-flow velocity (CBFV). This method is ideally suited for bedside evaluation of simultaneous cerebral haemodynamic changes while monitoring ICP in children, since other methods of measuring cerebral

blood-flow are invasive or involve radio-isotopes and cannot be used continuously or repeatedly. In an animal experimental model, Barzo *et al.* (1991) showed that at the lower range of autoregulation, changes in CBFV showed a strong correlation with cerebral blood-flow changes, and they suggested that non-invasive CBFV measurements could be a reasonable substitute for cumbersome or radio-isotopic measurements for patients with intracranial hypertension.

The aim of our study was to assess the cerebrohaemodynamic response to ICP increase in hydrocephalic children when there was clinical suspicion of reduced intracranial compliance or decompensation of their hydrocephalic state. Transcranial Doppler ultrasound was used to measure simultaneous CBFV change with ICP recordings during sleep.

Patients and method

Eight sleep studies were performed on seven patients (five boys, two girls), aged between 12 and 118 months. Their medical diagnostic background is set out in Table 1. All but one patient (case 5) had shunts. Four patients (4 to 7) had no symptoms of raised ICP and sleep recordings were performed to assess decompensation because of persistent or increased ventricular dilatation on neuro-imaging. The three patients who were symptomatic

TABLE I
Medical diagnostic background

Case	Sex	Age (mths)	Diagnosis	Indication for ICP monitoring
1	M	108	Myelomeningocele, shunted at birth; CT scan—slit lateral ventricles, isolated 4th ventricle	Intermittent headaches
2	F	118	Post-neonatal coliform meningitis, shunted; CT scan—slit lateral ventricles, isolated 4th ventricle	Deteriorating ataxic gait
3	F	25	Posthaemorrhagic, shunted aged 6 wks; secondary craniosynostosis, 1st skull morcellation aged 12 months, marked development delay; CT scan—slit lateral ventricles	Irritability and vomiting, awake ICP 6mmHg
4	M	37	Postpneumococcal meningitis, shunted aged 3 mths; deafness, seizures, delayed development	Increased ventricular dilatation
5	M	14	Posthaemorrhagic— <i>unshunted</i> , asymptomatic; mild delay in gross motor development	Persistent ventricular dilatation
6	M	34	Posterior fossa arachnoid cyst, cyst-peritoneal shunt aged 6 mths; asymptomatic, normal development	Persistent ventricular dilatation
7	M	12	Myelomeningocele, shunted aged 2 wks; asymptomatic	Mild increased ventricular dilatation

(1-intermittent headaches, 2-deteriorating ataxic gait, 3-irritability and vomiting) had slit-like lateral ventricles on CT scan and normal ICP levels on brief awake ICP measurements. One of them had a repeat study after a skull morcellation procedure.

ICP monitoring

Direct intraventricular pressure was measured in all patients through a frontal Rickham reservoir, using a non-displacement strain-gauge pressure transducer (Gaeltec Ltd.), which was calibrated against a sphygmomanometer before each study. A 23-gauge butterfly needle was percutaneously inserted in the reservoir with aseptic procedure and connected to the pressure transducer via a three-way tap. A continuous printout of ICP was obtained on a paper chart recorder. A separate reservoir is routinely inserted in almost all our patients with hydrocephalus to provide access for ICP measurement or emergency CSF drainage as required (Leggate *et al.* 1988).

ICP recordings for a total duration of 39.17 (mean 4.9, range 1.65 to 8.5) hours were obtained. Only spontaneous ICP measurements were used for analysis; any due to physiological stress (*e.g.* coughing, movement, *etc.* with an expected raised central venous pressure) were identified by an observer at the bedside and excluded

from analysis. We defined 'stable periods' as periods of unchanging mean ICP levels; 'unstable periods' included plateau and other abnormal waveforms or elevations of ICP which occurred spontaneously and did not include artefactual elevations due to coughing, *etc.* The mean ICP values over the periods of stable and unstable pressure were obtained from a review of the charted paper records. Mean basal ICP levels were calculated from two to four epochs of stable ICP states. The duration of unstable pressure periods was measured and the sum of these was calculated as a percentage of the total ICP recording for each individual study. The maximum mean ICP level during each unstable epoch was also obtained, and the type of pressure elevations—*i.e.* A/plateau, B or C waves—were characterised.

CBFV

CBFV was measured in the middle cerebral artery, using a 2MHz pulsed-wave hand-held probe attached to a portable Doppler unit (Decorder-Doptek Ltd, Chichester, UK). The middle cerebral artery was chosen for its accessibility and reliability, and was insonated through the temporal bone using the technique described by Aaslid *et al.* (1982). The Decoder performs real-time spectral analysis on the ultrasound signal and displays a spectrogram with 64 grey

TABLE II
Mean ICP during stable (basal) and unstable periods of individual sleep records

Case	Duration ICP record (hrs)	Mean basal ICP (mmHg)	N unstable periods	Duration unstable periods (hrs)	% Total ICP recording	Mean maximum ICP during unstable period (mmHg)	Type of intermittent pressure elevation
1	8.5	4.4	5	3.29	39.0	33.4	20 mins plateau wave to mean 58mmHg, B and C waves
2	2.2	9.0	3	0.54	24.5	32.3	B waves
3 pre-op	1.65	17.5	3	0.71	42.7	33.5	B waves and intermittent elevation to 30-35mmHg for 10-15 mins
3 post-op	5	16.7	1	0.25	6.0	24.3	Small C waves
4	3.88	14.7	3	0.79	20.2	31.3	Intermittent rise to mean max. 28-30mmHg for 5-6 mins
5	5.09	10.5	5	1.86	36.7	21.5	Intermittent rise to mean max. 19-25mmHg for 6-10 mins
6	7.7	16.4	2	0.55	7.0	24.0	Intermittent rise to mean max. 24mmHg for 4-15 mins
7	5.9	15.2	6	3.31	56.0	31.2	Intermittent rise to mean max. 25-30mmHg for 10-20 mins

levels in time increments of 5, 10, 20 and 40ms.

The Doppler signals were recorded on the two channels of a high-quality audio cassette deck (Yamaha KX500). The spatial peak temporal average intensity of the ultrasound beam measured in water was less than 100mWcm^{-2} . A remote-control box attached to the cassette deck allowed voice-dubbing of patient and ICP information onto tape.

When the optimal position for the Doppler probe had been identified, all subsequent CBFV measurements were made from this position and depth. All the Doppler recordings were performed by the same investigator (D.G.). CBFV recordings of one to two minutes were made at 10 to 15-minute intervals while the ICP was stable, and continuously during changing ICP states. The recordings were subsequently played back and analysed, and values of the time-averaged mean flow velocity (MFV), peak systolic (S), end-diastolic (D) velocities and the Pourcelot Resistance Index ($RI = (S - D)/S$) were measured. Each calculated value was obtained from the mean of at least five to 10 consecutive stable waveforms of good quality. The outline of the maximum velocity envelope was traced by hand, using a light pen, and the Doppler indices were calculated by software in the Decoder. This method allows accurate measurements to be made; background noise in the spectrogram could be ignored, as could waveforms distorted by patient or probe movement.

Assuming a constant vessel diameter, change in time-averaged MFV in response to hypercapnia suggests that the MFV provides a reliable index of mean volume flow (Kirkham *et al.* 1986). A close correlation has also been shown for percentage change in MFV and in cerebral blood-flow measured using intravenous xenon¹³³, although correlation for absolute measurements are less reliable because of wide inter-patient variations (Bishop *et al.* 1986).

The RI has been adapted as an index of cerebrovascular resistance (Pourcelot 1976, Bada *et al.* 1979), because RI increases as diastolic velocity (D) decreases with increasing distal resistance to flow. Archer *et al.* (1986) have demonstrated in healthy neonates a significant correlation between

TABLE III
Correlation (*r*) between ICP and Doppler indices in individual sleep records

Case	Duration CBFV record (hrs)	ICP/MFV		MFV/PSV	MFV/EDV	ICP/RI	
		<i>r</i>	<i>p</i>	<i>r</i>	<i>r</i>	<i>r</i>	<i>p</i>
1	5.17	-0.64	<0.001	0.57	0.96	0.89	<0.001
2	0.71	-0.46	<0.05	0.68	0.95	0.70	<0.001
3 pre-op	1.61	-0.24	NS	0.78	0.92	0.61	<0.001
3 post-op	5.25	0.58	<0.001	0.72	0.80	0.03	NS
4	3.75	-0.13	NS	0.77	0.985	0.41	<0.01
5	4.0	0.37	<0.01	0.96	0.93	0.69	<0.001
6	2.45	0.64	<0.001	0.86	0.94	0.13	NS
7	3.5	0.63	<0.001	0.91	0.96	-0.80	<0.001

ICP = intracranial pressure; CBFV = cerebral blood-flow velocity; MFV = mean flow velocity; PSV = peak systolic velocity; EDV = end diastolic velocity; RI = resistance index.

decreasing RI and decreased distal resistance which was due to hypercapnia-induced vasodilatation and increased cerebral blood-flow.

When it was possible to do so without disturbing the children's sleep, blood pressure was measured intermittently using the oscillometric method with a Dinamap machine. This allowed arithmetic calculation of the cerebral perfusion pressure (CPP = mean arterial pressure - ICP). Graphical plots of simultaneous ICP, CPP and CBFV changes over time were made for each individual study. Linear regression of Doppler indices with ICP change were assessed.

Results

Table II summarises the duration and mean ICP during stable (basal) and unstable (with intermittent ICP elevation) periods of each sleep recording. Basal ICP levels ranged between 4.4 and 17.5 mmHg; in six of the eight studies there were unstable periods of intermittent ICP elevation between 20 and 56 per cent of the total period of ICP recording. Table III summarises the duration of simultaneous ICP/CBFV recording and the correlations between ICP with MFV and RI for individual studies.

Decreased MFV response to ICP elevation (type I)

From the graphical plots of simultaneous

ICP/CPP/CBFV changes, two main patterns of MFV response were observed in association with episodic increased ICP during sleep. In four studies, increased ICP was associated with an over-all progressive decrease in MFV ($r = -0.44$, $p < 0.001$) (Fig. 1) and an increase in RI ($r = 0.64$, $p < 0.001$) (Fig. 2), which we will refer to as a type I response. In this group, MFV decreased as CPP decreased (over-all correlation: $r = 0.44$, $p < 0.001$). In three of these patients who were symptomatic, chronic CSF overdrainage with slit-ventricle syndrome was suspected. Figure 3 shows a graphical plot of simultaneous ICP/CPP/MFV/RI change during the sleep recording of patient 1, which illustrates the decreased MFV response associated with increased ICP and decreased CPP. Plateau/A and B waves were recorded in these three patients. Figure 4 is a graphical plot of a plateau wave, illustrating the marked decrease in MFV associated with reduced CPP to 30 mmHg during the sustained rise in ICP. With onset of the rapid ICP rise, there was a steadily decreasing MFV with increasing RI as ICP increased, with the trend reversing as ICP fell. A similar response was also observed during B waves. The fourth patient with mildly increased ventricular dilatation, who showed a less marked decreased MFV response, was thought to have deteriorating shunt function.

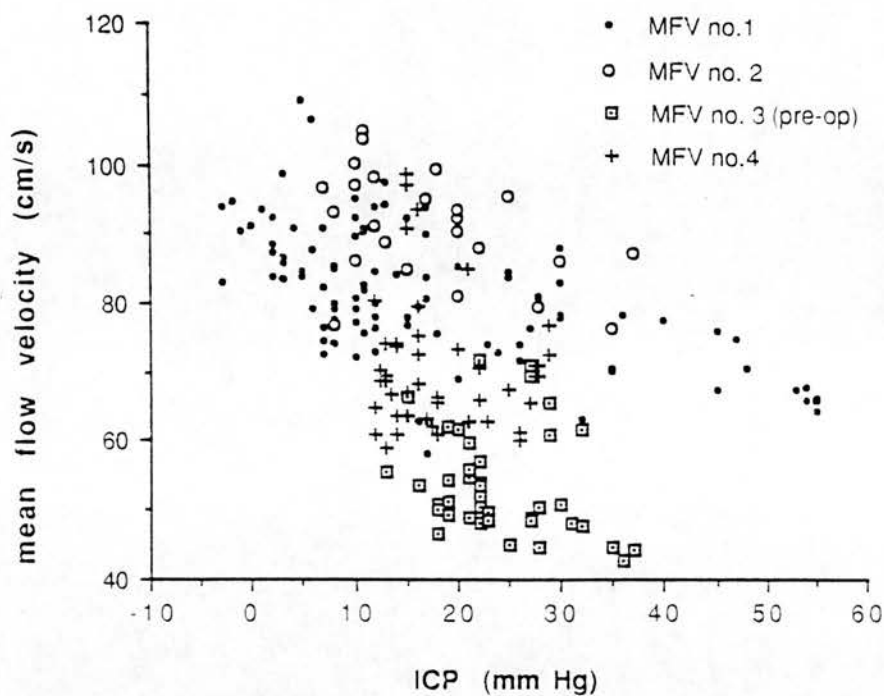


Fig. 1. Plot of mean flow velocity (MFV) versus ICP in four sleep studies which showed progressive decrease in MFV as ICP increased (type I response). Each patient is represented by a different symbol.

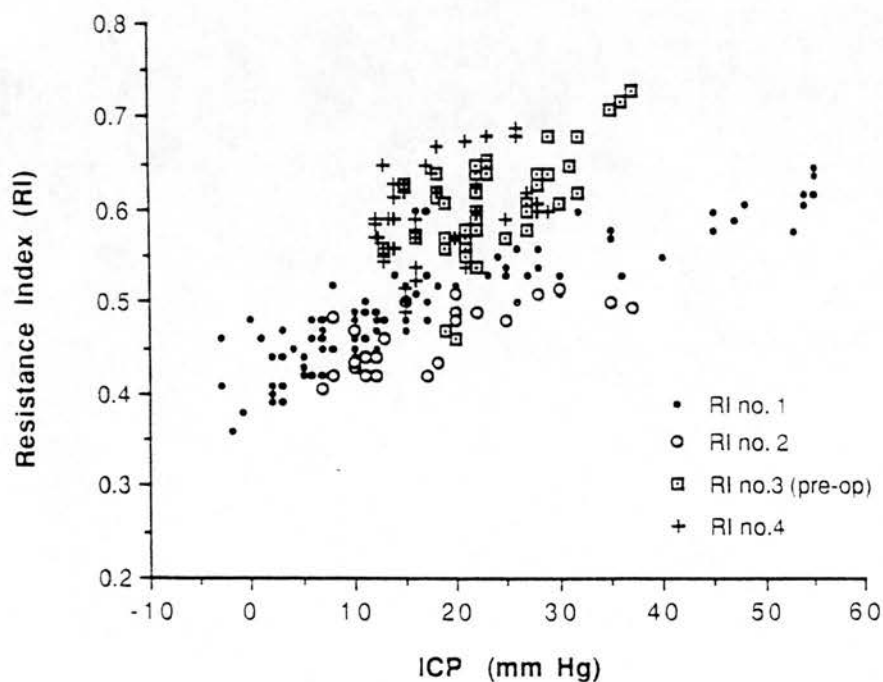


Fig. 2. Plot of resistance index (RI) versus ICP in four sleep studies with decreased MFV response to increase in ICP (type I response), associated with progressive increase in RI as ICP increased. Each patient is represented by a different symbol.

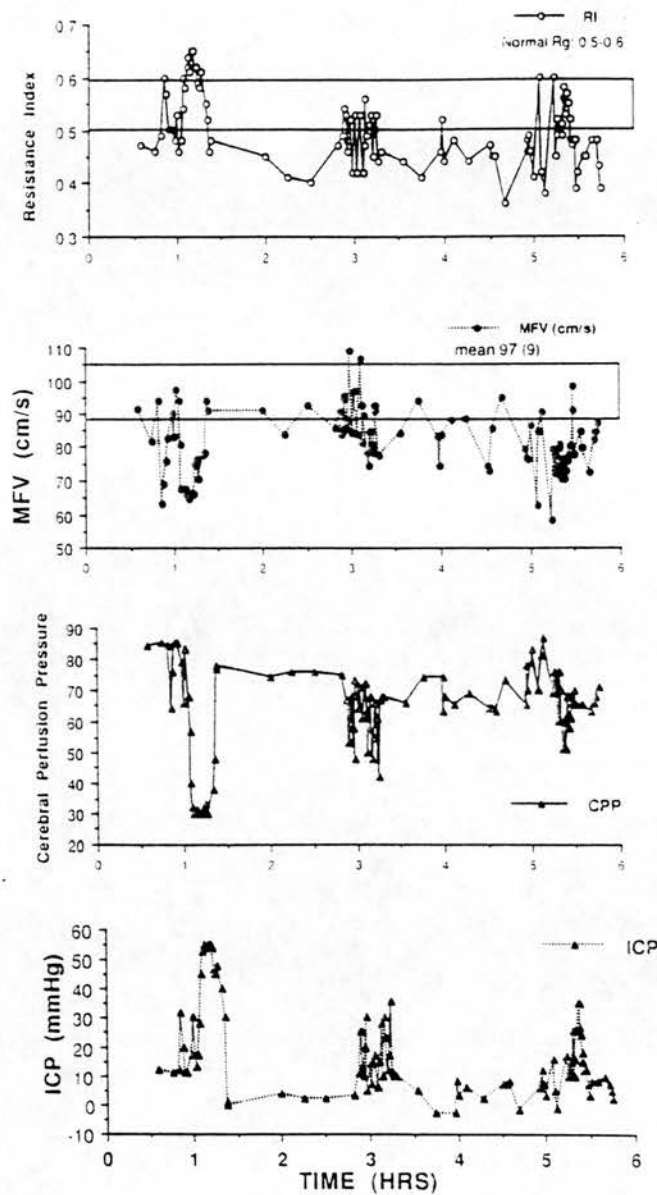


Fig. 3. Plot of simultaneous ICP, cerebral perfusion pressure (CPP), mean flow velocity (MFV) and resistance index (RI) during sleep study in case 1. It illustrates decreased MFV (type I) response with decreased CPP as ICP increased. Horizontal bands represent reported mean (± 1 SD) range of MFV and RI for patient's age.

Bilateral temporal decompression procedures (which involve removal of the calvarial side of the temporal bones) were performed on patients 1 and 2 and a skull morcellation procedure (removal of cranial sutures and repositioning of morcellated skull bones) was performed on patient 3 to enhance intracranial vault

volume in these three patients with slit ventricles, as overnight ICP and CBFV monitoring suggested limited intracranial compliance. The skull morcellation procedure can be performed only on young patients, usually up to a maximum age of three years. Shunt revision was performed on the fourth patient.

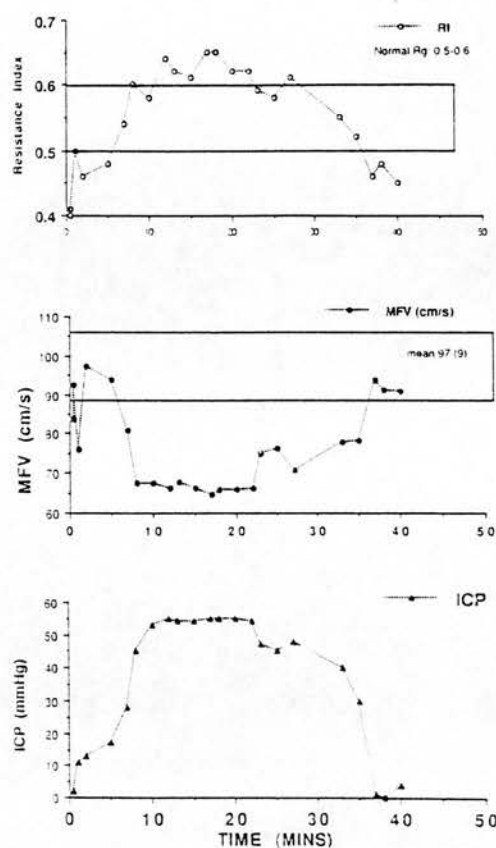


Fig. 4. Plot of simultaneous ICP, mean flow velocity (MFV) and resistance index (RI) during plateau wave, which shows marked progressive decrease in MFV and increase in RI as ICP increased. Horizontal bands represent reported mean (± 1 SD) range of MFV and RI for patient's age.

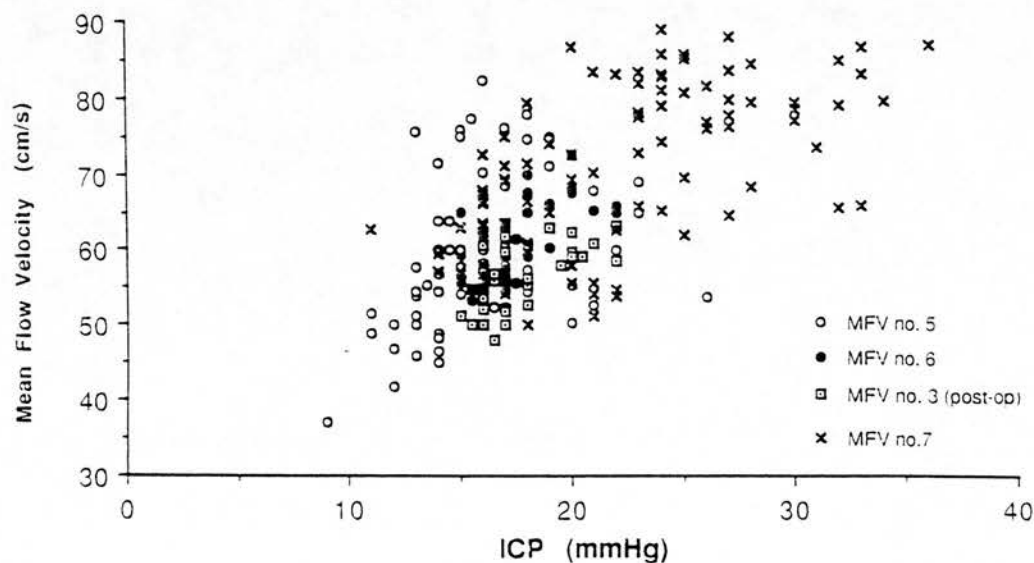


Fig. 5. Mean flow velocity (MFV) versus ICP in four sleep studies in which there was progressive increase in MFV as ICP increased (type II response). Each patient is represented by a different symbol.

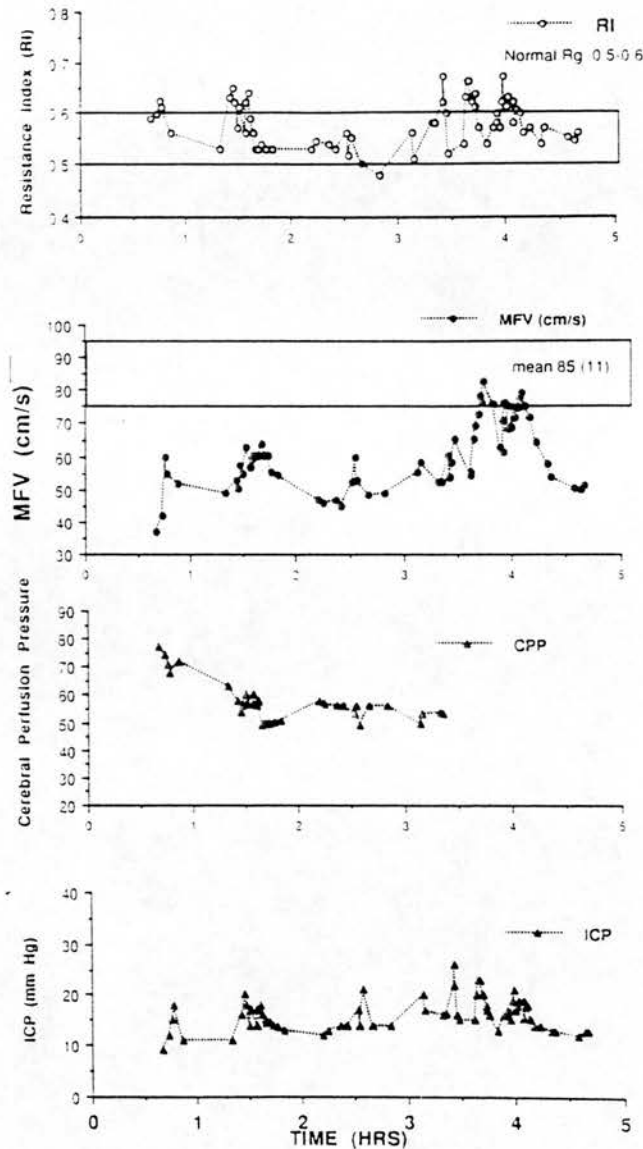


Fig. 6. Simultaneous ICP, cerebral perfusion pressure (CPP), mean flow velocity (MFV) and resistance index (RI) from sleep study of case 5, showing increased MFV and increased RI as ICP increased. Horizontal bands represent mean (± 1 SD) range of MFV and RI for patient's age.

Increased MFV response to ICP elevation (type II)

Another pattern of CBFV response with corresponding increased MFV when ICP increased ($r=0.65$, $p<0.001$) (Fig. 5), which we will refer to as a type II response, was observed from graphical plots in four studies. CPP data were available for three of these studies. There

was an over-all increase in MFV as CPP decreased ($r=-0.46$, $p<0.001$). Figure 6 shows a plot of simultaneous ICP/CPP/MFV/RI for patient 5, which illustrates the type II (increased MFV) response during a rise in ICP. In three of these studies, increased ICP was associated with slight or definite increase in RI, while in one patient (7), who also showed an increased

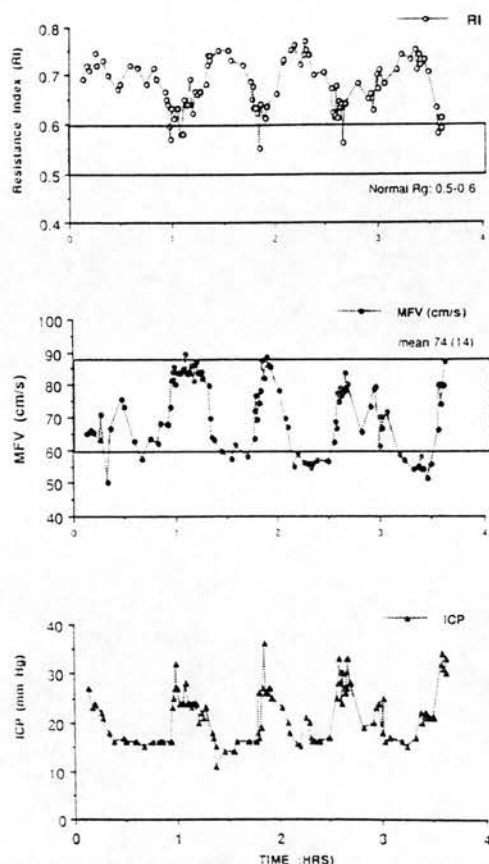


Fig. 7. Simultaneous ICP, mean flow velocity (MFV) and resistance index (RI) from sleep study of case 7, showing increased MFV response while RI decreased as ICP increased. Horizontal bands represent mean (± 1 SD) range of MFV and RI for patient's age.

MFV response, RI decreased as ICP increased (Fig. 7). None of these studies with an increased MFV response had sustained plateau or B ICP waves recorded; at most three had episodic elevations of 10 to 20 minutes duration to a mean maximum pressure of 20 to 30 mmHg, although the over-all duration of unstable ICP periods was a significant percentage of the total period of ICP recording for patients 5 and 7. A repeat study of patient 3, who previously had a type I (decreased MFV) response to increased ICP, showed improvement, with marked reduction in the percentage of unstable ICP periods, reduction in mean maximum ICP levels and a change to a type II (increased MFV) response to rise in ICP following a skull

morcellation procedure.

We felt that patient 5 had compensated arrested hydrocephalus, as he remained clinically well without a shunt, with little evidence of significant ischaemic effect, although periods of intermittent ICP elevations were seen in his overnight recording. At most recent follow-up nine months later, his head circumference remains on the 75th centile and he continues to make appropriate developmental progress, except for a mild five to six months delay in gross motor skills, which may be related to an intraventricular haemorrhage in his preterm neonatal period. Patient 6, who also showed a type II (increased MFV) response to rise in ICP, has also remained clinically asymptomatic, with normal developmental achievements for his age. Thus, although he has marked ventricular dilatation, no further shunt procedure was felt to be necessary.

The relationship between ICP and CBFV indices in hydrocephalic children involves examining not only the CBFV indices in response to changing ICP, but also changes in CBFV indices independent of ICP changes. During 'stable' ICP periods there were no marked fluctuations in CBFV indices, as can be seen for example in Figures 3, 6 and 7.

Plots of MFV against peak-systolic and end-diastolic velocities in each study showed that the change in MFV during the type I (decreased MFV) response was more closely related to change in end-diastolic velocity (range of correlation value, $r=0.92$ to 0.985) than to change in peak-systolic velocity (range of correlation value, $r=0.57$ to 0.78), suggesting that elevated ICP during these studies caused a more significant increase in distal resistance to flow. In these cases, therefore, the decreased MFV is more likely to reflect decreased perfusion as distal cerebrovascular resistance increases. During the studies with a type II (increased MFV) response, the change in MFV was equally related to change in end-diastolic velocity (range of correlation values, $r=0.8$ to 0.96) as in peak-systolic velocity (range of correlation value, $r=0.72$ to 0.96), suggesting that the type II response reflects an over-all increase in mean volume flow.

Discussion

Doppler flow velocities cannot provide absolute measurements of cerebral blood-flow and although we have shown reported normal ranges of MFV (Bode and Wais 1988) in our illustrations, this should not be interpreted as an indication of normal cerebral blood-flow because of wide interpatient variations and the lack of knowledge of true individual cerebral arterial cross-sectional diameters. However, with due caution, interpretation of CBFV changes can provide a reliable, non-invasive measure of cerebral perfusion changes in individual patients over a short period of time. A progressive decrease in MFV and increase in RI as ICP increases suggests a decreasing mean flow with increased distal resistance. Conversely, an increased MFV response suggests that mean flow is increased, despite a rise in ICP.

We think that in this study, change in MFV does provide a reliable index of mean volume flow changes over each individual recording, as the Doppler measurements were performed from a constant position and at a constant depth throughout, once the optimal position was selected at the beginning of each study. Thus measurement error of CBFV because of a varying angle of insonation is minimised. We have assumed that it is unlikely that there would be any significant change in the diameter of the middle cerebral artery to affect CBFV change during each study: first, there was no evidence of cerebral vascular disease in our young patients, and second, autoregulatory response occurs mainly through alteration of calibre in distal resistance vessels (Kato and Auer 1989), rather than in a major artery such as the middle cerebral artery.

As none of the studies with increased MFV response had MFV values over 100 cm/s, it is unlikely that vasospasm of the middle cerebral artery would have been responsible for the observed increase in MFV. A possible explanation for the increased MFV response to ICP rise may have been a progressive narrowing of the insonated artery (*i.e.* the middle cerebral artery) rather than a true increase in mean volume flow. While we have assumed that there are unlikely to be major diameter

changes in a major vessel such as the middle cerebral artery in our patients in response to ICP elevations during sleep, we accept that recent experimental studies have raised the possibility of some alteration in vessel calibre in response to local haemodynamic forces, haematocrit and arterial CO₂ (Brant *et al.* 1987, Melkumyants *et al.* 1989, Melkumyants and Baiashov 1990). It is thought in one study that up to one-third of total cerebrovascular resistance can be attributed to cerebral arteries of more than 150 μ m diameter (Faraci *et al.* 1987). However, in other studies of both humans and animals during reductions in systemic blood-pressure, the change in calibre of large cerebral arteries was found to be relatively small, generally less than 5 per cent (Radu and duBoulay 1976, Heistad *et al.* 1978, Kontos *et al.* 1978, Harder 1984). With continuous monitoring, although the errors introduced by an assumption of unchanging calibre may be significant, they are perhaps acceptable. Thus velocity changes at the point of insonation in the middle cerebral artery should reasonably reflect mean flow changes effected by changes in the distal resistance vessels.

A potential source of error for handheld intermittent Doppler recordings is inexact repetition of the angle of insonation, which may already be distorted in hydrocephalic patients if there is significant temporal-horn dilatation (Finn *et al.* 1990). Changes in absolute velocity indices such as the MFV, peak-systolic and end-diastolic velocities will be more significantly affected, while the RI, as a ratio, minimises this potential error. In practical terms, we endeavoured to maintain a constant angle by rigorously selecting only optimal clear signals from the same position at frequent intervals or continuously during changing ICP states, while rejecting signals distorted by movement. During normal sleep, even with the use of a headband to allow fixation of the transcranial probe, frequent adjustment for optimal signals and the exclusion of poor-quality or distorted waveforms by an experienced operator would still be required, as spontaneous head movements can easily dislodge the probe.

It has been established that cerebral blood-flow increases during REM sleep (Reivich *et al.* 1968, Sawayawa and Ingvar 1989), probably mediated by vasodilatation, so in patients with underlying defective CSF absorptive mechanisms the resulting increase in intracranial blood volume is inadequately buffered, producing a greater rise in ICP. Sustained plateau (A) waves are thought to occur as a result of autoregulatory responses in those with decreased intracranial compliance, elevated ICP and unstable CPP (Rosner and Becker 1984). In our study, assessment of the periods of elevated ICP, as a percentage of total recording, did not clearly separate those who showed a decreased MFV response from those with an increased response to rise in ICP. The mean duration of unstable ICP periods was 31.6 per cent for the group with decreased MFV response and 26.4 per cent for the group with increased response. For appropriate management, the important question is the clinical significance of these episodic ICP increases for each individual patient so that unnecessary surgical procedures can be avoided for those who can haemodynamically compensate adequately, while also seeking to prevent secondary ischaemic insult to those at risk.

In an earlier study, Minns (1991) found that patients with slit ventricles and high ICP spent significantly more of their sleep periods with compromised CPP levels compared with other groups of hydrocephalic patients. Prolonged mean transit time for cerebral isotope clearance, suggesting reduced circulatory reserve, was significantly related to reduced CPP as a result of raised ICP (Minns and Merrick 1989). Gibbs *et al.* (1984), using positron emission tomography, have reported that prediction of residual perfusion reserve from the ratio of cerebral blood-flow to blood volume was a reliable way of identifying patients with carotid artery occlusion who were most haemodynamically compromised. In our study, the type I (decreased MFV) response to rise in ICP with rise in RI suggests that raised ICP, which may be initiated by a small increase in cerebral blood volume, can lead to a substantial rise in cerebrovascular resistance and

result in diminished cerebral blood-flow, reflected by the decreased MFV. In experimental animals, Barzo *et al.* (1991) suggested that the decreased cerebrovascular resistance that accompanied the decreased cerebral blood-flow and CBFV was autoregulatory down to a perfusion pressure of 40mmHg. Below this level (*i.e.* with loss of autoregulation), they found a further increase in cerebrovascular resistance, which they suggested was due to intracranial hypertension blocking cerebral venous outflow. As a result of the increasing resistance, cerebral blood-flow and CBFV progressively diminished, despite maximal vessel dilatation.

During plateau/A and B waves, the markedly decreased MFV response suggests that circulatory reserve may be critical during these episodes. In an experimental cat model, Kato and Auer (1989) showed that when ICP was increased from 13 to 45mmHg by ventricular infusion of mock CSF, significant pial arterial dilatation of 40 per cent occurred. However, with further rise of ICP, no additional arterial dilatation occurred. Thus maximum cerebrovascular compensation has already occurred and any subsequent increase in ICP is likely to result in reduced perfusion. Our patients with a type I response, who showed decreased MFV with decreasing CPP, demonstrated this loss of haemodynamic compensation with progressive decrease of perfusion pressure, and were thus at greater risk of ischaemic insult from decreased blood-flow, especially those with reduced intracranial compliance, such as the three patients with slit ventricles. This type I response was abolished in patient 3 after an intracranial volume-enhancing procedure (skull morcellation), which should improve intracranial compliance and hence also perfusion reserve.

In those with a type II (increased MFV) response to rise in ICP, our data suggest that an appropriate cerebrovascular response to moderately increased ICP during sleep can occur through distal pial arterial dilatation and increased cerebral blood-flow to maintain adequate perfusion. This is more likely in patients who have adequate circulatory reserve, so a

type II response to rise in ICP may provide a means of identifying patients who are able to compensate haemodynamically for episodic pressure elevations, with little risk of ischaemic insult. During these studies, the MFV increased despite decreasing CPP due to an increase in ICP. This reinforces the view that evaluation of CPP change alone may not reliably predict those whose cerebral perfusion remains adequate, despite a rise in ICP.

The RI response may be variable, as change in distal cerebrovascular resistance will depend on other factors such as existing transmural pressure, vascular compliance and cerebral blood volume in the arterial and venous compartments. In three studies with an increased MFV response, distal resistance (RI) increased correspondingly as ICP increased; hence cerebral blood volume would probably not have been markedly increased. In patient 7, increased MFV was associated with a decrease in distal resistance during the rise in ICP, therefore there may have been a net increase in cerebral blood volume. Doppler flow velocities, however, do not quantitate absolute CBF, nor its ratio to blood volume; hence it would not be possible with this technique alone to make a reliable prediction of the overall effect on cerebrovascular resistance and net perfusion.

SUMMARY

The clinical importance of intermittent intracranial pressure (ICP) elevations during sleep in hydrocephalic children is unclear. Eight studies of continuous ICP monitoring with simultaneous cerebral blood-flow velocity (CBFV) measurements were recorded during sleep in seven hydrocephalic children aged between one and 10 years. ICP was measured directly through a frontal reservoir. There were two main patterns of CBFV change in response to raised ICP: a progressive decrease in mean flow velocity and increase in resistance index, suggesting impaired haemodynamic compensation to ICP elevation due to reduced circulatory reserve in patients with limited intracranial compliance; and an increase in mean flow velocity with raised ICP, suggesting that appropriate haemodynamic compensation with increased blood-flow can occur to maintain adequate cerebral perfusion in those with sufficient circulatory reserve. Simultaneous CBFV and ICP measurements may help to identify those with reduced circulatory reserve who are at greater risk of ischaemic insult from episodic increases in ICP.

RÉSUMÉ

Réponse en vitesse de circulation sanguine cérébrale aux élévations intermittentes de pression intracranienne durant le sommeil chez les enfants hydrocéphales

L'importance clinique des élévations intermittentes de pression intracranienne (ICP) durant le sommeil chez les enfants hydrocéphales n'est pas claire. Huit études d'enregistrement continu d'ICP avec une mesure simultanée de la vitesse de circulation sanguine cérébrale (CBFV) ont été effectuées durant le sommeil chez sept enfants âgés de un à 10 ans. L'ICP a été mesurée directement à travers un réservoir frontal. Il y avait deux distributions principales des modifications de la CBFV en fonction de l'élévation de l'ICP: une diminution progressive de la vitesse moyenne de circulation et un accroissement de l'index de résistance, suggérant une altération de la compensation hémodynamique à l'élévation de l'ICP, due à une réserve circulatoire réduite chez des patients à compliance

Studies of adult patients in coma (Hassler *et al.* 1988, Klingelhöfer *et al.* 1988) have reported a consistent increase in pulsatility of Doppler waveforms with decreased MFV and increased RI during major increase in ICP, *i.e.* equivalent to our type I (decreased MFV) response. Our results suggest, however, that in children with compensated hydrocephalus, appropriate haemodynamic response (increased MFV) to maintain adequate perfusion may occur during episodic moderately increased ICP during sleep. However, when intracranial compliance is limited, circulatory reserve may be critical, so simultaneous transcranial Doppler monitoring of CBFV with ICP may help to identify those patients who are at greater risk of ischaemic insult (those with decreased MFV response) from episodic increases in ICP. This may help in more appropriate selection of patients who will benefit from surgical procedures.

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Authors' Appointments

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intracranienne limitée; et un accroissement de la vitesse moyenne de circulation avec l'élévation de l'ICP, suggérant qu'une compensation hémodynamique appropriée avec circulation sanguine accrue peut se produire pour maintenir une irrigation cérébrale adéquate, permise par une réserve circulatoire suffisante. Des mesures CBFV et ICP simultanées pouvant aider à identifier les patients ayant une réserve circulatoire réduite, et qui sont plus exposés à une agression ischémique à partir d'élévation épisodique de l'ICP.

ZUSAMMENFASSUNG

Veränderungen der cerebralen Blutflußgeschwindigkeit durch intermittierende intracraniale Druckerhöhungen im Schlaf bei Kindern mit Hydrozephalus

Die klinische Bedeutung der intermittierenden intracraniellen Druckerhöhungen (ICP) im Schlaf bei Kindern mit Hydrozephalus ist unklar. Bei sieben Kindern im Alter zwischen einem Jahr und 10 Jahren wurden acht kontinuierliche ICP Aufzeichnungen mit simultanen Messungen der cerebralen Blutflußgeschwindigkeit (CBFV) im Schlaf durchgeführt. Der ICP wurde direkt über ein frontales Reservoir gemessen. Als Reaktion auf einen erhöhten ICP fanden sich zwei Muster von CBFV Veränderungen: ein progredienter Abfall der mittleren Flußgeschwindigkeit und eine Erhöhung des Widerstandes, was auf eine gestörte hämodynamische Kompensation der ICP Erhöhung durch verminderte zirkulatorische Reserven bei Patienten mit begrenzter intracranialer Compliance hinweist; und eine Zunahme der mittleren Flußgeschwindigkeit mit erhöhtem ICP, was darauf hinweist, daß eine angemessene hämodynamische Kompensation mit einer Blutflußzunahme zur Aufrechterhaltung einer adäquaten Hirnperfusion bei den Kindern mit ausreichenden zirkulatorischen Reserven vorkommen kann. Simultane CBFV und ICP Massungen können dazu beitragen, die Kinder mit verminderter zirkulatorischer Reserve herauszufinden, die ein höheres Risiko für einen ischämischen Insult durch episodische ICP Erhöhungen haben.

RESUMEN

Respuesta de la velocidad del flujo sanguíneo cerebral a la elevación intermitente de la presión intracranial durante el sueño en niños hidrocefálicos

No está clara la importancia clínica de las elevaciones intermitentes de la presión intracranial (PIC) durante el sueño en niños hidrocefálicos. En siete niños de uno a 10 años de edad se registraron las mediciones de la velocidad del flujo sanguíneo cerebral (VFSC) durante el sueño y se monitorizó de forma continua la PIC en un total de ocho estudios. La PIC se midió directamente por medio de un reservorio frontal. Se observaron dos patrones de cambios en la VFSC como respuesta a un aumento de la PIC: una disminución progresiva en la velocidad media del flujo y un aumento en el índice de resistencia, lo que sugiere una alteración en la compensación hidrodinámica a la elevación de la PIC debida a una circulación de reserva reducida en pacientes con una complianza intracranial limitada; y también un aumento en la velocidad media del flujo con el aumento de la PIC, lo que sugiere que puede tener lugar una compensación hemodinámica apropiada, con aumento del flujo sanguíneo, con el objeto de mantener una perfusión cerebral adecuada en los casos con una reserva circulatoria suficiente. La medición simultánea de VFSC y de PIC puede ayudar a la identificación de aquellos casos con reserva circulatoria reducida, que están con un riesgo mayor de insulto isquémico a consecuencia de un aumento episódico de la PIC.

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26 — A Volume—Blood Flow Velocity Response (VFR) Relationship Derived from CSF Compartment Challenge as an Index of Progression of Infantile Hydrocephalus

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A. James W. Steers¹

Summary. Optimal management in childhood hydrocephalus requires prevention of secondary ischemic damage and reliable indication for surgical treatment to prevent long-term shunt related complications. Transcranial Doppler ultrasound provides a noninvasive means of monitoring cerebrohemodynamic response. Cerebral blood flow velocity (CBFV) and intracranial pressure (ICP) was measured during 38 CSF taps in 11 patients (6 neonates, 5 children). The Resistance Index ($RI = S - D/S$) (where S — peak systolic velocity and D — end diastolic velocity) decreased significantly ($P < .001$) after all taps, mainly due to a larger percentage increase in diastolic velocity and mean flow velocity (MFV) which increased in 89% of taps, suggesting a significant reduction in cerebrovascular resistance and increased flow after cerebrospinal fluid (CSF) depletion. There was a significant positive correlation of RI to ICP ($r = 0.63$, $P < .001$) in older children. Exponential decay of RI with volume depletion allows estimation of "critical" volume buffering capacity. Serial volume flow velocity response (VFR) in individual infants may indicate progression or arrest of the hydrocephalic process and may help to select more precisely those who will benefit from surgical intervention.

Keywords. Cerebral blood flow — Intracranial pressure — Transcranial doppler — Hydrocephalus

Introduction

It is important to differentiate progressive hydrocephalus in children from those cases which will arrest spontaneously or those that may require only temporary cerebrospinal fluid (CSF) removal. The aim of management is to prevent further ischemic damage due to increasing ventricular dilatation and

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raised intracranial pressure (ICP) while avoiding unnecessary surgical procedures and the long term complications of shunting such as craniocerebral disproportion from overdrainage. Single measurements of ICP, even when repeated on separate occasions, do not provide information on intracranial dynamics and compliance to separate those who have reached a critical point on the exponential intracranial volume — pressure curve with limited available volume buffering capacity. Shulman and Marmarou (1971) and Miller et al. (1973) have characterised ICP dynamics with the Pressure-Volume Index (PVI) and the Volume-Pressure Response (VPR), respectively, using volume challenge techniques. However, infants with hydrocephalus were reported to have elevated PVI compared to predicted normal values (Shapiro et al. 1985) due to altered brain biomechanics as a result of the hydrocephalic process.

The Doppler principle can be applied to measurement of cerebral blood flow velocity (CBFV). Hill and Volpe (1982) first reported a decrease in pulsatile flow of anterior cerebral arteries in infantile hydrocephalus using Doppler ultrasound. Resistance Index ($RI = (S - D)/S$ where S — peak systolic velocity and D — end diastolic velocity) as an index of cerebrovascular resistance adapted by Bada et al. (1979) from Pourcelot's Index of Resistance (Pourcelot 1976) was significantly raised. Transcranial Doppler ultrasound techniques (Aaslid et al. 1982) now provide a noninvasive means of repeated assessment of cerebrohamodynamic change for all ages.

The aim of our study was to examine a direct blood flow velocity response to volume manipulation in children with hydrocephalus, as ICP rise causes ischemic damage due to its secondary effect on cerebral perfusion. A volume — flow velocity response (VFR) could theoretically estimate residual volume buffering capacity before an "ischemic" point is reached and serial VFRs should therefore indicate progression or arrest of the hydrocephalic process. There have been no previous reports on sequential CBFV change with volume manipulation in hydrocephalic children.

Patients and Methods

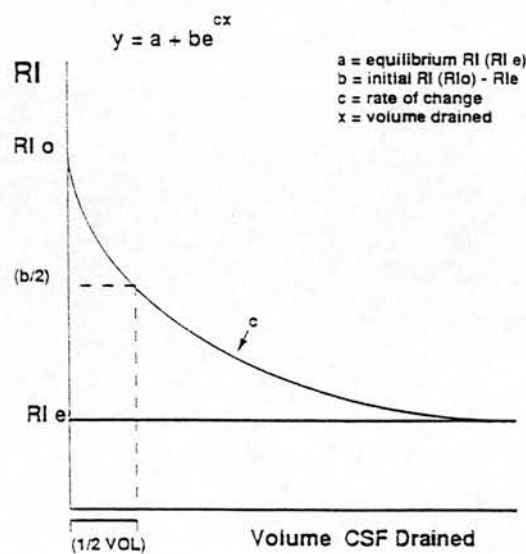
Eleven patients (7 males, 4 females) with hydrocephalus of varying etiology, age range 35 weeks gestation–118 months, were assessed. Table 1 describes their clinical details and indications for CSF taps. They are divided into two groups. Group I were all neonates ($n = 6$) while group II patients were between 12–118 months old, because the "normal" range of cerebral Doppler indices are age dependent with less change after the first year of life (Bode 1989; Chaddock and Seibert 1989). Four patients in group II had existing ventricular peritoneal shunts in situ. Indications for CSF taps were signs or symptoms of raised ICP, evidence of increasing ventricular dilatation, e.g., from imaging evidence (ultrasound or computed tomography (CT) scan) or increasing head circumference measurements in young infants.

A total of 38 CSF taps (33 in group I; 5 in group II) were performed. ICP was measured directly through a ventriculostomy reservoir where available

Table 1. Clinical details and indications for CSF taps

Patient	Age	Etiology	Clinical
Group 1: Neonates			
(1) LF	C.A — 2 weeks	Perinatal Infection	Progressive vent dilation
(2) MG	Term	X-linked Congenital	Gross hydrocephalus
(3) NB	Term	Occip encephalocele	Vent dilat postrepair
(4) FR	35/40	Posthemorrhagic	Vent dilat and p.cysts
(5) RA	Term	Prenatal PHH	Progressive vent dilatation
(6) JM	Term	Myelomeningocele	Vent dilat postrepair
Group 2: Children			
(7) CM	17 months	PHH	Vent dilatation, mild dev delay, not shunted
(8) CJ	4 years	PHH	Broken VP shunt
(9) PB	12 months	Myelomeningocele	Increased vent dilat
(10) LH	10 years	Post-meningitis	Slit vent, ataxia
(11) IF	14 months	PHH	Vomiting, ICP raised

C.A. corrected age; vent dilat. ventricle dilatation; occip. occipital; PHH. posthemorrhagic hydrocephalus; p.cysts. porencephalic cysts; VP. ventriculo-peritoneal; ICP. intracranial pressure



[1/2 VOL = volume when $RI = RI e + (RI o - RI e)/2$]

Fig. 1. A predicted exponential curve fit $y = a + be^{cx}$ for serial observed Resistance Index (RI) decay with volume depletion during CSF taps. Half-volume = $-0.7/c$, i.e., the volume drained when 1/2 change in RI has occurred

(Leggate et al. 1988) or through ventricular ($n = 4$) or lumbar ($n = 1$) puncture, using a non-displacement method with a strain gauge pressure transducer (Gaeltec) connected to a butterfly or spinal needle. CSF was drained in 1-ml increments with repeated ICP measurements until a normal value for age range was achieved (Minns et al. 1989).

Continuous CBFV in the middle cerebral artery (MCA) insonated through the thin temporal squamous bone (methodology as described by Aaslid 1982) was recorded throughout the tap using pulsed-wave Doppler (Decoder — Doptek Ltd., Chichester, UK) with a 2 or 4 MHz probe. This allowed unhindered access for ICP measurement and CSF removal; the MCA was chosen also for accessibility, easy identification, and reliability using the transcranial approach. CBFV signals were recorded onto audiotape and reviewed separately; only good quality consecutive waveforms were analyzed. Incorporated computer calculation of RI, MFV (time averaged mean of maximum velocity envelope) were used to characterise the Doppler waveforms and a mean value of at least 10 waveforms was obtained. RI was mainly used to minimize error in CBFV measurement due to variability in angle of insonation.

Pre- and post-tap ICP, RI, MFV, PSFV (peak systolic flow velocity) and EDFV (end diastolic flow velocity) were compared using Student's paired *t*-test. Plots of RI (y) against volume CSF drained (x) were fitted to an exponential curve $y = a + be^{cx}$ (a = equilibrium RI, i.e., RI_e , atb = initial RI i.e. RI_o , b = change in RI i.e., $RI_o - RI_e$, and c = rate of exponential decay). (see Fig. 1). A "half-volume" when half the change in RI had occurred was obtained by calculation, i.e., "half-volume" = $-0.7/c$.

Results

Tables 2 and 3 summarise the pre-and post-tap ICP and Doppler indices from group 1 and 11 patients. In all taps there was, as expected, a statistically significant change in ICP and also a highly significant decrease in RI ($P < .001$) after volume withdrawal. After 34 taps (89%), there was an increase in MFV — this was statistically significant only in group 1. The percentage increase in EDFV was greater and more significant than PSFV change in both groups, thus the decrease in RI was due primarily to improved diastolic flow. There was a significant positive correlation of RI to increased ICP ($r = +0.63$, $P < .001$) in group 11 patients — see Fig. 2. In the neonatal group, overall correlation between RI and ICP was poor but in two neonates who had sufficient repeated measurements, there was a significant correlation ($r = +0.61$ and 0.40 , $P < .001$) in their individual measurements.

Data were available for 36 serial RI and volume plots. Figure 3 shows the sequential parallel decrease in RI and ICP with CSF volume depletion from a patient who was not shunted. Only two taps did not fit an exponential curve. RI was significantly lower in the children compared to the neonates. The rate of exponential decay was slowest in the child (aged 17 months) who was not shunted, i.e., largest "half-volume," suggesting increased volume buffering in

Table 2. Doppler and ICP change pre- and post-CSF taps in Group I (neonates) patients

Doppler indices and ICP	No. of paired obs	Pre-tap	Post-tap	% Change	P value
Mean RI (SD)	33	0.78 (.06)	0.69 (.06)	11.5%	<.001
Mean MFV (SD) cm/s	33	45.2 (9.4)	52.6 (9.2)	16.3%	<.001
Mean PSFV (SD) cm/s	23	82.8 (8.9)	87.4 (10.8)	5.6%	<.02
Mean EDFV (SD) cm/s	23	15.8 (5.4)	25.1 (5.7)	59%	<.001
Mean ICP (SD) mmHg	31	9.8 (2.6)	4.6 (1.6)	53%	<.001

Table 3. Doppler and ICP changes pre- and post CSF taps in Group II (children) patients

Doppler indices and ICP	No. of paired obs	Pre-tap	Post-tap	% Change	P value
Mean RI (SD)	5	0.61 (.08)	0.5 (.06)	18%	<.001
Mean MFV (SD) cm/s	5	54.9 (17)	66.5 (16)	21%	NS
Mean PSFV (SD) cm/s	5	86.0 (26)	93.7 (24)	9%	NS
Mean EDFV (SD) cm/s	5	33.2 (11)	45.7 (15)	37.7%	<.05
Mean ICP (SD) mmHg	5	15.4 (3.8)	5.8 (1.8)	62.2%	<.02

Fig. 2. Plot of RI versus ICP during CSF taps in Group 11 patients (>12 months old) shows significant positive correlation ($r = 0.63$, $P < .001$)

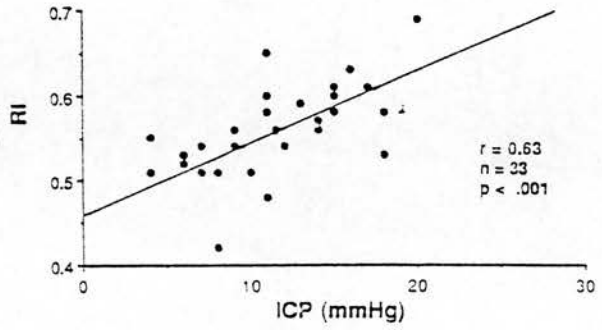


Fig. 3. Plot of parallel RI and ICP change against volume CSF drained in patient CM with unshunted hydrocephalus

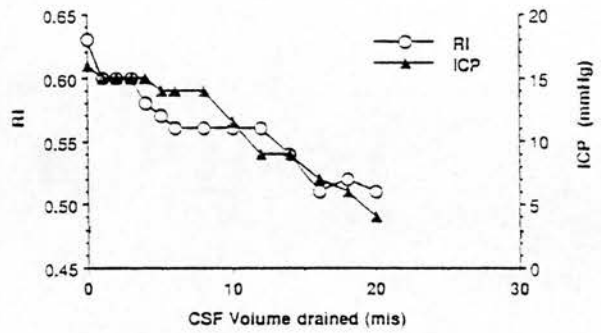


Fig. 4. Plot of predicted RI (open triangle) and observed RI (closed circles) against CSF volume drained in child (CM) with unshunted hydrocephalus shows slow exponential decay in RI

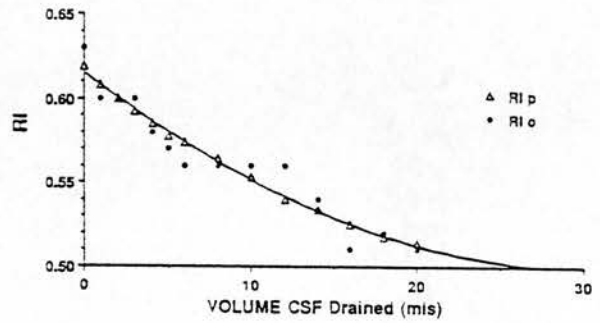
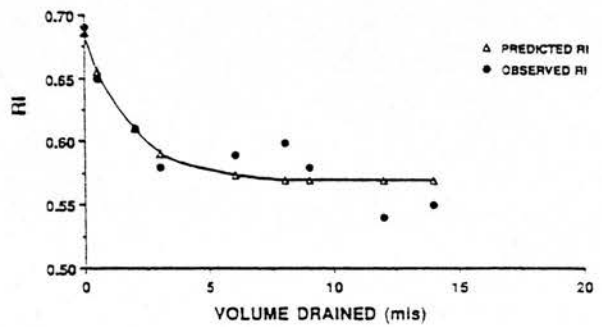


Fig. 5. Plot of predicted and observed RI against volume drained in a child who presented with a broken shunt shows rapid exponential decay in RI



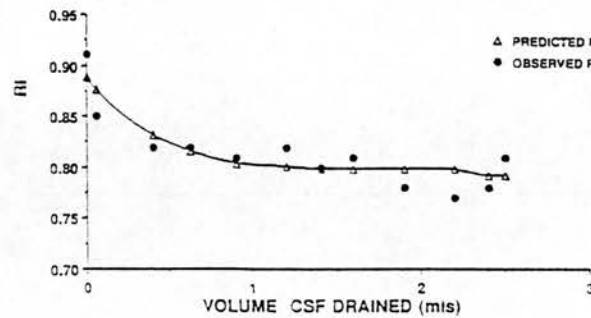


Fig. 6. Plot of predicted and observed RI with volume drained in a neonate (NB) who was not shunted

Table 4. 'Half-volumes' and RI change with volume depletion during CSF taps

Patients	No. obs (n)	Equilibrium RI RI _e (SD)	Change in RI (RI _o - RI _e) SD	Half-vol (mls)
Children				
Non-shunted	1	0.47	0.15	11.9
Shunted	4	0.48 (0.1)	0.13 (.03)	2.1 (1)
Neonates				
Not shunted	2	0.72 (0.1)	0.13 (.05)	1.97
Shunted later	24	0.69 (0.04)	0.08 (.03)	1.75 (2)
Post shunt	3	0.66 (0.03)	0.08 (.04)	0.81 (0.3)

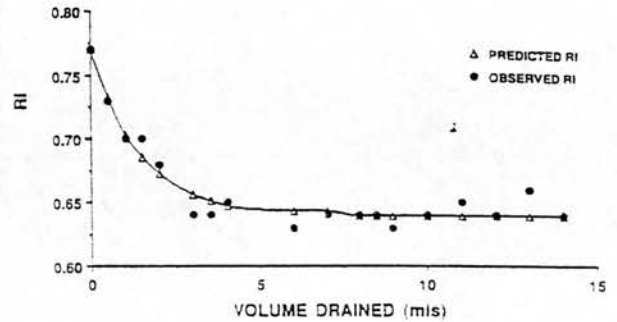
the absence of a ventricular shunt. Figure 4 shows a plot of observed and predicted RI against volume CSF drained in this patient. Figure 5 shows a plot of predicted and observed RI decay with volume depletion in a child who had a broken shunt and Figure 6 shows a plot from a neonate who was not shunted. "Half-volumes" in the shunted children and in neonates with or without shunts were not significantly different (Table 4). Three further taps were performed in one neonatal patient whose initial ventriculo-peritoneal shunt blocked. Figure 7 shows a plot of RI versus volume change after this initial shunt. Equilibrium RI was lower compared to pre-shunt values, suggesting that shunting alters volume-flow response even though shunt function was not adequate.

Discussion

In hydrocephalus, progressive ventricular dilatation and raised ICP causes secondary ischemic damage from impairment of cerebral perfusion with changes of macro- and microvascular compression and distortion (Wozniak et al. 1975). Compliance estimations do not directly relate perfusion responses at various stages of the hydrocephalic process. Change in cerebral perfusion pressure (CPP) is assumed from the calculation $CPP = MAP - ICP$ (where MAP is mean arterial pressure) whenever ICP is altered.

Shapiro et al. (1985) suggest that PVI is increased in hydrocephalic children due to change in brain biomechanics, which becomes a perpetuating factor that

Fig. 7. Plot of predicted and observed RI with volume drained from a CSF tap performed after initial unsuccessful ventriculo-peritoneal shunting in a neonatal patient (R.A.). Equilibrium RI was lower than pre-shunt values



allows ventricular enlargement to occur by encouraging storage of volume. This, however, does not distinguish those patients whose hydrocephalic process arrests spontaneously before significant ischemic insult occurs and whose indications and optimal timing for intervention remain controversial. CSF shunting procedures disrupt normal CSF absorption and most patients with CSF shunts become shunt-dependent and thus remain at risk from long-term complications such as ventriculitis and slit ventricle syndrome.

Archer et al. (1986), using hypercapnia-induced increase in CBF, showed a significant correlation with decrease in RI as an index of distal cerebrovascular resistance. Our results suggest that CSF depletion reduces ICP and distal resistance to CBF, as there was a highly significant reduction in RI which was due to a more significantly increased EDFV after CSF taps. Previous studies reporting decrease in RI after CSF taps have not utilized direct ICP measurements (Van Bel et al. 1988) or have not related RI to ICP and volume manipulation (Seibert et al. 1989).

We have shown that decrease in RI with volume depletion generally followed an exponential curve similar to the ICP/volume-relationship (VPR or PVI), suggesting that there is similarly a "critical" volume buffered before blood flow response is significantly altered. In neonates and young infants with wide open sutures, single ICP measurements do not predict those who require shunting. There was a poor overall correlation of ICP to RI in the neonatal group and those with elevated RI did not necessarily have increased ICP (Hill and Volpe 1982). Thus some infants may have considerably raised cerebrovascular resistance with reduced perfusion without significantly raised ICP. Repeated RI measurements can provide an estimate of cerebrovascular resistance and its rate of change with volume manipulation (VFR) for individual patients. If RI remains elevated compared to the normal range for age and serial VFR shows deterioration or no change with time, surgical intervention would be indicated, as there is no development of natural arrest. Repeated RI measurements showing an improvement toward normal values for age would encourage non-interventional management. Noninvasive transcranial Doppler monitoring of cerebrohemodynamic change in hydrocephalus, in particular serial change with volume manipulation (VFR), may help to select more precisely those who require intervention.

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Intracranial pressure and cerebral arterial flow velocity indices in childhood hydrocephalus: current review

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Abstract Because of its noninvasive and repeatable nature, Doppler ultrasound has been increasingly used to assess changes in cerebral haemodynamics in infants and children with hydrocephalus. There is general agreement that a direct correlation exists between the intracranial pressure (from experimental, fontanometric and direct measurement evidence) and the resistance index. In addition, this increasing index has been predominantly due to a reduction in the end-diastolic velocity. Stable ventriculomegaly is

associated with normal pulsatility. The cerebral blood flow velocity parameters change significantly following CSF drainage by tapping or shunting. The measurement of intracranial pressure and cerebral blood flow velocity are currently the best ways of assessing the need for CSF diversion and monitoring subsequent shunt function.

Key words Intracranial pressure · Cerebral blood flow velocity · Hydrocephalus · Childhood

Introduction

There has been increasing clinical use of Doppler ultrasound as a noninvasive means of assessing cerebral perfusion changes in infants and children with hydrocephalus since Hill and Volpe [14] first reported increased pulsatility of the cerebral arterial flow velocity (CAFV) waveforms in 11 hydrocephalic infants. Since then Doppler studies, either from duplex scans through the anterior fontanelle in young infants or transcranial Doppler (TCD) scans in older infants and children have revealed varying effects on waveform pulsatility and variable contributions of peak systolic (PSV) or end-diastolic velocities (EDV) to pulsatility changes. Few study groups have reported on intracranial pressure (ICP) levels in their patients, either from direct or from transfontanelle measurements. Most have made assumptions about the likely presence or absence of raised ICP (RICP) from the clinical state. However, clinical symptoms and signs of RICP in hydrocephalus are highly variable and unreliable [17]. There have also been few attempts to study dynamic

CAFV changes in response to intracranial volume changes. The purpose of this paper was firstly to review previous studies on CAFV changes, along with our own experience in an attempt to clarify the consistent findings, and secondly to consider further dynamic studies that may have a more helpful role in predicting the patients who will benefit from de novo shunting or revision of existing shunts.

Cerebral arterial flow velocity indices

The two pulsatility indices most commonly applied in hydrocephalic patients have been the Pourcelot resistive index (RI), which is the $(PSV - EDV)/PSV$ and the Gosling pulsatility index (PI), which is the $(PSV - EDV)/\text{mean velocity}$. Both indices, being ratios, thus minimise the error in estimating true velocity due to a varying angle of insonation. This may be more important in hydrocephalus, as Finn et al. [7] have shown that vascular

anatomy may be significantly distorted by ventricular enlargement and a small angle of insonation cannot be assumed. It is unfortunate, however, that some confusion has arisen because the term 'pulsatile index' has been commonly used in the paediatric literature to mean both the RI and PI. Although both indices essentially provide a measure of the 'pulsatility' or sharpness of the waveform shape, they differ numerically, and each component of these indices may be differently affected by changes in distal impedance, pump forces or cerebrovascular compliance. It is thus important to clarify which index has been used as well as to analyse which component of the CAFV waveform contributed most significantly to observed changes in pulsatility.

Studies reporting no diagnostic value of pulsatility indices in hydrocephalus

Most studies have found increased pulsatility in patients with progressive or 'symptomatic' hydrocephalus. Only two studies [2, 12] have concluded that pulsatility indices did not contribute significant diagnostic information in hydrocephalus. Grant et al. [12] did not find significantly raised RI in their hydrocephalic patients but only 3 of their 10 patients had overt clinical signs of RICP. Anderson and Maw [2] reported increased pulsatility in only 31% of their hydrocephalic patients requiring shunting when mean pulsatility was also generally increased in all their patient groups except those with ventriculomegaly without haemorrhage or shunts. In stable/non-progressive ventricular dilatation without RICP, cerebral perfusion is not compromised, and we would not expect to find a raised pulsatility index. However, as ICP was not measured in either study it is not clear whether some of these patients may have been in a stable state without RICP.

Studies relating ICP to CAFV pulsatility

Experimental evidence

Seibert et al. [24] measured ICP directly in four dogs from a frontal lobe fiberoptic monitor (Camino) with simultaneous Doppler recordings. They found a direct correlation between ICP, cerebral perfusion pressure and RI.

Transfontanelle pressure measurements

Hill and Volpe [14] reported elevated transfontanelle pressure (measured with a Ladd fontanometer) in all but 2 of their patients. However, they concluded that ventriculomegaly was a more critical factor than RICP in the pathogenesis of impaired flow, as these two patients also

had an elevated Pourcelot RI and the four patients with the most marked ventriculomegaly had the most markedly elevated RI. Hanlo [13] and Horikawa [15] have also reported a direct relationship between increased pulsatility and raised transfontanelle pressure.

Direct ICP measurements

Data from 13 patients reported by Chaddock et al. [4] suggest a reliable linear relationship between RI and ICP beyond the normal range for RI (between 0.45 and 0.6) obtained by TCD study. Our own data [8, 9, 11] support a reliable correlation between RI and ICP, in older children as a group or for individual neonatal patients. Pople et al. [22] have also found a significant correlation between the Gosling PI and intraventricular pressure in 14 patients whose pressure levels were estimated by tapping their shunt system.

Relationship between ventricular dilatation and CAFV pulsatility

A number of studies have shown that stable ventriculomegaly is associated with normal pulsatility [2, 5, 16, 21]. A corresponding trend between increased RI with increasing ventricular dilatation was reported by Lui et al. [18], in common with Hill and Volpe's findings. However absent diastolic flow also occurred in two infants with only moderate ventricular dilatation, and RICP was suspected to be a contributory factor, although ICP was not measured in this study. Horikawa [15] showed that after shunting there was a rapid fall in CAFV pulsatility while ventricular size was only slightly reduced, thus suggesting that changes in pulsatility were mainly affected by ICP.

CAFV changes before and after drainage (taps and shunts)

All studies of CAFV before and after CSF drainage by ventricular taps or shunting [5, 8, 9, 14, 15, 21, 24, 25] have consistently shown that pulsatility is significantly decreased after effective CSF drainage.

Effect of PSV and EDV on waveform pulsatility Index

Two studies which analysed components of the RI reported that the increased RI in hydrocephalus was due to increased PSV [1, 25] which the authors attributed to in-

creased cerebrovascular compliance. ICP was not measured in either of these two studies. However, other recent studies have shown that increased pulsatility is due to marked decrease in EDV [5, 16] as the significant fall in pulsatility after CSF drainage is due to a significant increase in EDV. Our data [8, 9] support the idea that the increase in EDV is of greater significance. It thus suggests that the RI is a reliable measure of distal cerebrovascular resistance.

Use of Doppler Indices in clinical management

Monitoring shunt malfunction

Shunt malfunction is associated with raised ICP, as most ventricular shunts are either totally or mostly pressure regulated. Raised pulsatility (both RI and Gosling's PI) has been shown to be a reliable indicator of shunt malfunction [4, 22]. In 41 patients with shunt malfunction RI decreased from 0.71 ± 0.1 to 0.53 ± 0.12 following revision, while 11 patients with functioning shunts had RIs of 0.47 ± 0.05 [4]. Of the 63 children admitted with suspected shunt blockage, 18 of the 32 cases with surgically confirmed blocked shunts had a Gosling PI value more than 2 standard deviations above the mean for their age for asymptomatic shunted children [22]. Only 1 of the 31 cases not requiring surgical intervention had a value outside the normal range.

Assessment of patients requiring shunting

Chaddock et al. [3] reported a mean RI of 0.84 in 46 neonates with symptomatic or progressive ventriculomegaly requiring shunts, which decreased to 0.72 after shunting. Horikawa [15] and Nishimaki [20] have also found similar RI values, suggesting RI values > 0.8 as criteria for shunting or judging shunt effectiveness in young infants. The RI values obtained from our neonatal and older patients before and after de novo shunting or revision are also in a similar range, supporting this as a reliable and reproducible index. In general, RI values persistently above 0.8 for neonates and young infants and 0.65 for children suggest that ICP may be elevated. In 24 patients (7 days to 14 years) Norelle et al. [21] reported mean Gosling PI values of 1.06 for those with stable ventriculomegaly, 1.72 in those with symptoms prior to shunt placement, and 1.02 after shunt placement. We agree with Chaddock's group that, as there is a wide variation of normal and an overlap between normal and abnormal values, the RI is a useful measurement on an individual basis, particularly for following a patient's course.

Using duplex ultrasound, Huang and Chio [16] monitored sequential ventricular size and anterior CAFV in 14 infants. Only patients in group I who had an elevated RI before shunting derived benefit, while the other group, who did not have a significantly raised RI before shunting, did not benefit from the procedure. Surprisingly, at operation ICP measured from the lateral ventricles before shunting was not significantly different between the two groups. The authors suggest that the pulsatility index can be useful to differentiate progressive hydrocephalus from atrophic ventriculomegaly, which does not benefit from shunting. In our experience it is especially important in neonates, as ICP levels which are not grossly raised, such as 8 mmHg, can be associated with impaired CAFV indices.

Dynamic studies of CAFV changes

During volume manipulation

Dynamic studies of ICP changes with volume manipulation have been widely used to assess intracranial compliance and CSF outflow resistance as criteria for shunting. Since a major concern for RICP is the secondary ischaemic insult that may occur, it could be more clinically useful to study directly the haemodynamic changes. As RI has been shown to correlate reliably with ICP, it may be a useful index to assess simultaneous haemodynamic changes during volume manipulation in a similar manner to the exponential relationship between intracranial volume and ICP. In a single illustrated case with posthaemorrhagic ventricular dilatation, Drayton and Skidmore [6] showed that during therapeutic drainage of CSF by lumbar puncture, the Gosling PI appeared to have an exponential pattern of decline, decreasing sharply at the beginning of the drainage and rapidly reaching an equilibrium level before the end of the drainage. We have examined the pattern of decline in RI in 16 patients sequentially during ventricular taps; all but 6 taps could be fitted to an exponential model [9, 19]. Figure 1 shows the observed RIs obtained sequentially during CSF withdrawal from an exponential curve $y = a + be^{cx}$. Theoretically, this *volume-bloodflow velocity response (VFR)* allows estimation of a 'half-volume', i.e. the volume of CSF withdrawn when half the observed change in RI has occurred. This may provide an index of volume buffering reserve, i.e. the volume of CSF drained before significant haemodynamic change is observed. To date no other studies investigating dynamic changes in CAFV indices have been reported. Most studies described previously have been devoted to CAFV changes before and after drainage procedures; none has examined sequential changes. We suggest that further

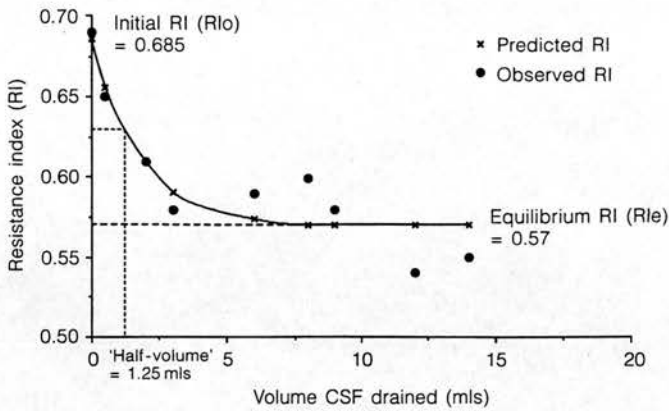


Fig. 1 Sequential observed and predicted RIs during CSF withdrawal from a ventricular reservoir in a 4-year-old patient who presented with a broken shunt. Predicted RIs are obtained from a fitted exponential curve $y = a + be^{cx}$, where a = equilibrium RI (RI_e), $a + b$ = initial RI at beginning of tap (RI_o), b = change in RI ($RI_o - RI_e$). Theoretically this allows estimation of a 'half-volume', i.e. the volume of CSF drained when half the change in RI ($b/2$) has occurred. It suggests that after only a small volume of CSF (1.25 ml) was drained, a significant haemodynamic flow velocity change was observed

investigation of this nature may be more useful in seeking to predict more reliably those patients who will benefit from long-term shunting.

Spontaneous episodic ICP changes during sleep

Spontaneous episodic elevations in ICP have long been recognised to occur during sleep in hydrocephalic patients. The clinical importance of these elevations in ICP has been unclear. During eight recordings of ICP and simultaneous CAFV changes during sleep in seven patients we observed that there were mainly two patterns of CAFV changes [10]. In four recordings the mean velocity decreased with increasing ICP, while in the other four recordings the mean velocity increased during increase in ICP. As the episodic ICP elevations in sleep are thought to be due to spontaneous changes in CBF and volume during the phase of rapid eye movement sleep, the increased mean velocity response may represent adequate

haemodynamic compensation. However, in those who showed a decrease in mean velocity together with an increasing RI in response to increasing ICP, cerebral perfusion may be progressively impaired. This may suggest limited cerebrovascular reserve and inadequate haemodynamic compensation during these events. Simultaneous CAFV changes in response to ICP increase may help to determine the patients who are thus at greater risk of ischaemic insult. This could be useful for evaluating those with 'arrested' hydrocephalus who present with subtle or chronic symptoms.

Conclusion

In summary, review of the literature to date has shown largely consistent findings that the pulsatility indices correlate with RICP in active hydrocephalus. Although Doppler assesses blood flow velocity, measurement of ICP together with CAFV changes will be most likely to represent the best current indication for CSF drainage on the premise that raised ICP impairs cerebral perfusion. Along with the use of ICP and CAFV indices as described, new indices are being assessed. A new index, the *trans-systolic index* described by Hanlo, Gooskens and Peters is being investigated as a possible index of compliance (personal communication). The '*volume-bloodflow velocity response*' (*VFR*) may provide a means of predicting volume-buffering reserve in individual patients as an index of progression or arrest of the hydrocephalic process. Recent work on cerebral venous velocity changes in posthaemorrhagic hydrocephalus [23] may also contribute to a better understanding of the disturbed cerebrohaemodynamics associated with ventricular dilatation.

In conclusion, much work is still required in understanding the complex cerebro- and hydrodynamic processes in hydrocephalus, and reliable indications for shunting are still required.

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